Comparative Effectiveness Review
Number 250

Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2025 Update

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

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If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

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Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2025 Update

Structured Abstract

Objectives. To update the evidence on benefits and harms of cannabinoids and other plant-based compounds to treat subacute and chronic pain in adults and adolescents using a living systematic review approach.

Data sources. Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases, and reference lists of included studies were searched to April 28th, 2025.

Review methods. We grouped studies based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio and by product type: *synthetic, purified (plant-derived product consisting of a single cannabinoid, e.g. dronabinol or CBD), or extracted (from whole plant, containing multiple cannabinoids).* We conducted random effects meta-analyses and categorized magnitude of benefit (large, moderate, small, or no effect [less than small]).

Results. Three new randomized controlled trials (RCTs) (n=90, 81, and 93) and three new observational studies (N=741, 148, and 96) were added for this annual update; no study addressed subacute pain or adolescents. One new RCT compared plant-derived topical hemp seed oil or diclofenac 1% gel versus placebo for knee osteoarthritis and one new RCT compared purified THC:CBD:cannabinol (CBN) versus placebo for diabetic neuropathy. Both of the cannabis product types evaluated in these trials were new for this review. The third new, head-to-head RCT compared purified inhaled comparable THC to CBD ratio (6.3% THC and 8% CBD) cannabis, 5 mg oxycodone tablets, or both for fibromyalgia. Since the inception of this living review, from 6,304 total abstracts identified, 29 RCTs (in 30 publications) (N=2,579) and 15 observational studies (N=49,453) of cannabinoids have been included; no study evaluated kratom. Studies were primarily short term, and 48 percent enrolled patients with neuropathic pain. Comparators were primarily placebo or usual care. Strength of evidence (SOE) for all comparisons and outcomes was low unless indicated otherwise.

Compared with placebo, extracted, comparable ratio THC to CBD oral spray was associated with a small decrease in pain severity (7 RCTs, N=878, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI] −0.95 to −0.19, I^2=39%; SOE: moderate); improvement in overall function favored the cannabis product but was slightly below the threshold for a small effect (6 RCTs, N=616, 0 to 10 scale [negative values indicate improved function], MD −0.42, 95% CI −0.73 to −0.16, I^2=32%; SOE: moderate) versus placebo. There was no difference in likelihood of study withdrawals due to adverse events (WAEs). There was a large increased risk of dizziness and sedation, and a moderate increased risk of nausea (dizziness: 6 RCTs, N=866, relative risk [RR] 3.57, 95% CI 2.42 to 5.60, I^2=0%; sedation: 6 RCTs, N=866, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%; and nausea: 6 RCTs, N=866, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%).

Synthetic and purified high THC to CBD ratio products were associated with a small improvement in pain severity versus placebo (8 RCTs, N=507, 0 to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I^2=64%), with no effect on overall function or disability. There was a moderate increase in risk of WAEs (6 RCTs, N=487, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%), a moderate increase in risk of sedation (5 RCTs, N=458, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%), and a large increase in risk of nausea (4 RCTs, N=425, RR 2.12, 95% CI 1.09 to 3.96; I^2=0%). There was also moderate SOE for a large increase in risk of dizziness (4 RCTs, N=425, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%).

Synthetic or purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, I^2=20%; SOE: moderate), greater likelihood of pain response (4 RCTs, N=334, RR 0.84, 95% CI 0.62 to 1.10, I^2=0%; SOE: moderate), or improved function (3 RCTs, N=272, standardized mean difference [SMD] 0.11, 95% CI −0.14 to 0.41, I^2=0%; SOE: moderate) versus placebo, and combined oral THC plus CBD (~1:2 ratio) was not associated with decreased pain intensity (2 RCTs, N=123, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%), greater likelihood of experiencing ≥30 percent improvement in pain (2 RCTs, N=123, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%), or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80) versus placebo.

Evidence (including observational studies) on whole-plant cannabis, topical CBD, other cannabinoids (including one new RCT of a THC:CBD:CBN product and one new RCT of hemp seed oil), comparisons with active noncannabis treatments (including one new RCT of cannabis vs. opioids) or between cannabis-related products, and impact of cannabis on use of opioids remained insufficient. Evidence was not available on important harms such as psychosis, cannabis use disorder, and cognitive effects.

Conclusions. Low- to moderate-strength evidence suggests small improvements in pain (mostly neuropathic) and moderate to large increases in common adverse events (dizziness, sedation, nausea) with extracted, comparable THC to CBD ratio and synthetic or purified high THC to CBD ratio products versus placebo during short-term treatment (1 to 6 months). Low- to moderate-strength evidence suggests that low THC to CBD ratio products may not be associated with improved outcomes versus placebo. Evidence for whole-plant cannabis and other comparisons, outcomes, and plant-based compounds was unavailable or insufficient to draw conclusions.

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Executive Summary

Main Points

This is the fourth and final annual update of a living systematic review addressing the effectiveness and harms of plant-based treatments for chronic and subacute pain in adults and adolescents. The first systematic review was published in October 2021, and the first, second, and third updates were published in September 2022, August 2023, and September 2024, respectively. As this review was "living," it used methods to identify and synthesize recently published literature and adapt its scope on an ongoing basis. Included plant-based compounds were those that have potential analgesic effects as well as the potential for addiction, misuse, and serious adverse effects.

Studies of cannabis-related products were grouped based on their tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio using the following categories: comparable THC to CBD, high THC to CBD (including THC only), and low THC to CBD (including CBD only). Since the third annual update of the systematic review published in September 2024, three new randomized controlled trials (RCTs) and three new observational studies were added, for a total of 29 RCTs (in 30 publications) and 15 observational studies. Two new RCTs were placebo-controlled—one evaluated plant-derived topical hemp seed oil or diclofenac 1% gel for knee osteoarthritis[1] and one evaluated purified topical THC:CBD:cannabinol (CBN) for diabetic neuropathy.[2] The cannabis product types evaluated in both new placebo-controlled RCTs were both new to this review. The third new RCT compared purified inhaled cannabis (6.3% THC and 8% CBD), 5 mg oxycodone tablets, or both for fibromyalgia.[3] The new observational studies evaluated various (low, comparable, or high THC to CBD ratio) products.[4-6] In patients with chronic (mainly neuropathic) pain with short-term treatment (4 weeks to <6 months), the living review found:

- Extracted, comparable THC to CBD ratio oral spray is probably associated with small improvements in pain severity (strength of evidence [SOE]: moderate) and overall function versus placebo (SOE: moderate). There may be no increase in risk of serious adverse events (SOE: low) or withdrawal due to adverse events (WAEs) (SOE: low). There may be a large increased risk of dizziness and sedation (SOE: low) and a moderate increased risk of nausea (SOE: low).
- Synthetic and purified THC (high THC to CBD) may be associated with small improvement in pain severity (SOE: low), but with increased risk of WAEs (SOE: low), sedation (SOE: low), and nausea (SOE: low) versus placebo. Synthetic and purified THC is probably associated with a large increased risk of dizziness (SOE: moderate).
- Low THC to CBD ratio oral products (synthetic or purified CBD alone, or combined purified THC plus synthetic CBD in ratio ~1:2) may not be associated with improved pain and function versus placebo (SOE: moderate for CBD alone and low for THC/CBD). THC plus CBD is probably associated with large increased risk of nausea (SOE: moderate).
- Other key adverse event outcomes (psychosis, cannabis use disorder, cognitive deficits) and outcomes related to use of opioids were not reported or evidence was insufficient to draw conclusions.
- We did not identify any evidence that met criteria for this review on other plant-based compounds such as kratom.

Background and Purpose

Cannabinoids are a group of compounds that are active in cannabis; the two main cannabinoid are THC and CBD. THC has demonstrated analgesic properties,[7,8] although its psychoactive effects and the potential for development of use disorder may limit its suitability as an analgesic. Cannabinoids may also be associated with serious harms, including those related to potential for use disorder or physiological withdrawal. The purpose of the systematic review is to evaluate the evidence on benefits and harms of cannabinoids and similar plant-based substances (e.g., kratom) to treat chronic or subacute pain on an ongoing basis. This report updates the original 2021 systematic review on cannabis and other plant-based treatments for chronic pain in adults.[9] In the 2023 update, the scope was expanded to include subacute pain and adolescents. Using a living review approach, the literature was monitored quarterly for new studies, and the systematic review was updated annually.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Effective Health Care Program Methods Guide (https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide), as described in the full report. Searches for this update covered publication dates from database inception to April 28th, 2025. The original review focused on adults with chronic pain.[10] With input from a Technical Expert Panel, the scope for the 2023 update was expanded to include adolescents and subacute pain. We included RCTs and comparative observational studies of minimum 4 weeks duration that assessed cannabinoids or kratom for noncancer chronic and subacute pain. Cannabinoids were categorized according to their THC to CBD ratio (comparable, high, low) and type (plant-derived [included whole plant, extracted or purified products] or synthetic). Strength of evidence was assessed as low, moderate, high, or insufficient, and magnitude of effect was assessed according to Table A. Estimates that were below the threshold for a small effect were categorized as "no effect."[11,12]

Table A. Definitions of effect sizes

Effect Size	Definition
No effect/trivial effect	• Below thresholds for small effect
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.
Note: For pain and function, negative values for MD indicate improved outcomes; for other outcomes, positive values for MD indicate improved outcomes.

Results

The included RCTs are described in Table B and the included observational studies are described in Table C. There were six new studies added since the prior annual update. There were two new placebo-controlled RCTs. One (n=90) compared plant-derived topical hemp seed oil or diclofenac

1% gel versus placebo for knee osteoarthritis.[1] Hemp seed oil is a new cannabis product for this review; it primarily consists of polyunsaturated fatty acids and does not contain THC, but has small traces of CBD. The other (n=93) evaluated purified topical THC:CBD:CBN in a 3.25:0.32:0.65 ratio versus placebo for diabetic neuropathy.[2] CBN, also new to this review, is a THC metabolite/oxidative byproduct that is mildly psychoactive and may have analgesic and anti-inflammatory effects. Due to the inclusion of CBN and the topical mode of administration, this product was considered separately from the oral or sublingual high THC to CBD ratio products previously included in the living review. The third new, head-to-head RCT (n=81) evaluated purified, inhaled comparable THC to CBD ratio (6.3% THC and 8% CBD) cannabis, 5 mg oxycodone tablets, or both for fibromyalgia.[3] All of the new observational studies (n=741, 96, and 148) included patients with various chronic pain conditions and evaluated various low, comparable, or high THC to CBD ratio cannabis products.[4-6] One new observational study (n=96) focused on the association between cannabis use and improvement in various chronic pain and mental health conditions.[6] The second new observational study (n=148) compared various whole plant preparations (cannabis oil, dried flower, and combination oil and flower) in people with fibromyalgia.[5] The third new observational study (n=741) compared various cannabis formulations in people with mixed chronic pain conditions.[4] The new studies did not change the main findings of the living review. Although two new RCTs each found a new cannabis product type (hemp seed oil and topical THC:CBD:CBN) associated with improved pain versus placebo, the SOE for these products was insufficient due to evidence being limited to single trials with small samples and methodological shortcomings.[1,2]

Table B. Characteristics of included randomized controlled trials of cannabinoids for chronic pain in adults

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
THC to CBD Ratio	Comparable[a]	High	Low	NA - other cannabinoids
Source	Extracted Purified	Synthetic Purified Extracted	Synthetic Purified Extracted Unclear	Extracted Purified
N Studies	**8** (1 new)[b]	13	7 (1 topical, 1 sublingual, 4 oral, 1 unclear)	**3** (2 new)[b]
Comparator (Study Count)	Placebo (7); 5 mg oxycodone or a combination of 5 mg oxycodone and inhaled cannabis (1)	Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low THC to CBD ratio (CBD or purified THC/CBD) (2)	Placebo (7); Dronabinol (2); Low THC to CBD ratio (CBD or purified THC/CBD (2); ≥97% purified low THC to CBD (1:6) sublingual oil (1); 5% or 10% CBD gel (unclear if synthetic or plant-based) (1)	Placebo (3); diclofenac 1% gel (1)

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
Route of Administration, Formulation (Study Count)	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl (7); Purified cannabis capsules inhaled using a vaporizer, 150 mg per capsule (1)	Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)	Oral capsule, 5 mg synthetic CBD (2); Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1) 5% or 10% CBD gel, unclear if local or systemic (1)	Oral oil, 50 mg/ml CBDV (1); Topical hemp seed oil, concentration NR (1); Topical THC:CBD:CBN oil in a 3.25:0.32:0.65 ratio (1)
Dosing Regimen	Oromucosal spray: Final mean dose 23 mg THC/21 mg CBD daily Inhaled cannabis: Maximum of three 150 mg capsules per day in week 1, increasing up to five capsules	Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day Dronabinol (Namisol®[a]) tablet: 3 to 8 mg 3 times daily, titrated. Final dose NR Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Capsule: 2.5 -12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily	Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2) Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2) Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD) Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR) CBD gel: 20 mg of 5% or 10% gel applied on each side, total dose 20-40 mg daily	400 mg CBDV daily. Final dose NR Topical hemp seed oil: 10 drops daily (dose NR) THC:CBD:CBN oil: 1-2 drops for mild pain; 3-4 drops for for moderate pain; 5-6 drops for severe pain

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
Risk of Bias	25% high, 63% moderate, 12% low	8% high, 46% moderate, 46% low	43% high, 43% moderate, 14% low	100% moderate
Total Randomized	963	1,028	568	224
Age, Mean Years	53	54	54	57
Female, %	71%	62%	60%	51%
Non-White,[c] %	1.6% (2)	5.3% (4)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1); Fibromyalgia (1)	NPP (9); Fibromyalgia (2); Visceral pain (1); Headache (1);	NPP (3); MS (1); OA (2); Temporomandibular (1); Unspecified (1)	NPP (2), OA (1)
Baseline Pain Score, Mean (Range)[d]	6.89 (6.4 to 7.30)	6.75 (4.00 to 8.67)[e]	6.01 (4.67 to 7.40)[f]	4.77 (2.54 to 6.28)
Study Duration	4 to 15 weeks	4 to 47 weeks	4 to 16 weeks	4 to 12 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; CBN = cannabinol; MS = multiple sclerosis; NA = not applicable; NPP = neuropathic pain; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; THC = tetrahydrocannabinol.

[a] All products were nabiximols.

[b] Two trials are included in both the THC and CBD columns, as they compared THC to CBD, CBD/THC, and placebo.

[c] (n) = number of studies reporting this characteristic at baseline.

[d] Scores were standardized to a 0 to 10 scale.

[e] Mean pain score includes median scores for 1 study (6 vs. 6).

[f] Mean pain score includes median scores for 1 study (5.2 vs. 6.1).

Note: Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

Table C. Characteristics of included observational studies of cannabinoids for chronic pain in adults

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear, mixed, or various	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice) or mixed cannabinoids	Extracted	Synthetic (nabilone)	Extracted vs. synthetic	Extracted
N Studies	**11** (3 new)[b]	1	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (2); other cannabinoids (5)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol	Long-acting opioids (MME 69.4 [SD 38.9] mg/day)
Route of Administration, Formulation	Unreported (any available allowed, patient's choice) (6); inhaled or oral prescribed cannabis (5)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
Dosing Regimen	None specified (9) Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1) Final median dose of 25 mg THC and 20 mg CBD (1)	None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day	None specified; final mean dose 3 mg/day	None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day	None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day
ROB	55% high, 45% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	47,179	431	156	674	1,310
Age, Mean Years	52	49	61	46	51
Female, %	56%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (10)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic noncancer pain (10) Fibromyalgia (1)	Chronic noncancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
Baseline Pain Score, Mean (Range)[c]	5.90 (4.60 to 7.47)[d]	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)	4.32 (4.31 to 4.33)
Study Duration, Weeks (Range)	12 to 208	52	26	24	24

Abbreviations: CBD = cannabidiol; LAO = long acting opioid; MME = morphine milligram equivalents; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; SD = standard deviation; THC = tetrahydrocannabinol.
[a] Patients could choose any medicinal product they preferred in these studies.
[b] Includes three new studies for this review.
[c] Scores were standardized to a 0 to 10 scale.
[d] Mean includes median scores for 2 studies
Note: Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

Tables D and E summarize the findings of the review. Other prioritized adverse events (cannabis use disorder [CUD], psychosis, cognitive deficits) and the impact on the use of opioids for chronic pain, were not reported in the RCTs.

Table D. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted, Oromucosal Spray	Potential effect (4)[b] [✓]	Small effect (7) [✓✓]	No effect[c] (6) [✓✓]
High THC – Synthetic or Purified, Oral	Insufficient (3, 1 new)	Small effect (8, 1 new) [✓]	No effect (4) [✓]

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
High THC – Extracted, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Extracted CBD, Topical	No evidence	Insufficient (1)	No evidence
Low THC – Synthetic or Purified, Oral[d]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (3, 1 new)[e]** [✓✓]
Low THC – Synthetic CBD Plus Purified THC, Oral[f]	**No effect (2, 1 new)[e]** [✓]	**No effect (2, 1 new)[e]** [✓]	**No effect (1)[e]** [✓]
Low THC – Sublingual CBD/THC, Extracted	No evidence	Insufficient (1)	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	**Insufficient (1 new)[e]**	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[g]	No evidence	Insufficient (1)	No evidence
Other cannabinoids – Hemp Seed Oil, Topical	No evidence	**Insufficient (1 new)[e]**	**Insufficient (1 new)[e]**
Other Cannabinoids – THC:CBD:CBN, Topical	No evidence	**Insufficient (1 new)[e]**	No evidence

Abbreviations: CBD = cannabidiol; CBN = cannabinol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] ≥30% improvement from baseline
[b] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[c] The pooled difference of -0.42 (95% CI -0.73 to -0.16) was just below the threshold for a small effect.
[d] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[e] Text is bolded to indicate that the strength of evidence has changed.
[f] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[g] Comparison was "usual care."
Text that is red indicates that a new study has been added. Color is used for visual emphasis only.
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [✓] = low, [✓✓] = moderate, [✓✓✓] = high.

Table E. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Comparable THC/CBD – Extracted, Oromucosal Spray	No effect (5) [✓]	No effect (3) [✓]	Large effect (6) [✓]	Moderate effect (6) [✓]	Large effect (6) [✓]
High THC – Synthetic or Purified, Oral	**Moderate effect (6, 1 new)[a]** [✓]	Insufficient (2, 1 new)	Large effect (4, 1 new) [✓✓]	**Large effect (4, 1 new)[a]** [✓]	Moderate effect (5, 1 new) [✓]
High THC – Extracted, Oral	Large effect (1) [✓]	Insufficient (1)	Large effect (1) [✓]	No evidence	No evidence
Low THC – Extracted CBD, Topical	No evidence	No evidence	No evidence	No evidence	No evidence

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Low THC – Synthetic or Purified CBD, Oral[b]	Insufficient (4, 2 new)	Insufficient (2, 1 new)	**No effect (3, 2 new)[a]** [✓]	**Insufficient (2 new)[a]**	**No effect (3, 2 new)[a]** [✓]
Low THC – Synthetic CBD plus Purified THC, Oral[c]	**Insufficient (2, 1 new)[a]**	**Insufficient (2, 1 new)[a]**	**Potential effect (2, 1 new)[a, d]** [✓]	**Large effect (2, 1 new)[a]** [✓✓]	**Potential effect (2, 1 new) [a, d]** [✓]
Low THC – Sublingual CBD/THC, Extracted	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[e]	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)
Other cannabinoids – Hemp Seed Oil, Topical	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – THC;CBD:CBN, Topical	No evidence	No evidence	No evidence	No evidence	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

[a] Text is bolded to indicate that the strength of evidence has changed.

[b] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.

[c] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.

[d] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.

[e] Comparison was "usual care."

Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [✓] = low, [✓✓] = moderate, [✓✓✓] = high.

Limitations

Key limitations of the evidence base relate to the limited ability to provide strong, reliable, estimates of effect due to: (1) inadequate sample sizes or numbers of studies, (2) narrowness of enrolled populations (primarily chronic neuropathic pain, with mean age 53 years; see Tables C and D), with no evidence on subacute pain or adolescents, (3) lack of evidence or inadequate evidence on extracted high THC to CBD products, whole-plant cannabis products, and extracted or nonoral low THC to CBD products; comparisons with other active interventions or different cannabis-related products; and other plant-based compounds including kratom, and (4) inconsistent reporting of important outcomes such as dosage, pain response, overall function or

disability, effect on opioid use, and longer-term adverse events, such as CUD, psychosis, and cognitive deficits. In addition, the applicability of findings may be reduced in specific settings, including the United States, due to the unavailability or unclear availability of studied cannabis products. These limitations affect both the stability and applicability of the findings.

Implications and Conclusions

Select individuals with chronic neuropathic pain may experience small short-term improvements in pain with some cannabis products, but the impact on moderate or long-term outcomes is unknown. Improvement in pain intensity was small with high and comparable THC to CBD ratio products, though there was insufficient evidence to determine effects on likelihood of a pain response (e.g., ≥30% improvement in pain). Compared with placebo, these interventions resulted in greater risk of common adverse events (dizziness, nausea, sedation); high THC to CBD products were also associated with increased risk of study WAEs. Low THC to CBD products, including CBD alone, were not associated with improved pain or function. Evidence for other interventions, including kratom, was insufficient or unavailable. As the strength of this evidence was mostly low, more data are needed to improve confidence in cannabis as a treatment for various chronic pain-related conditions, for specific cannabis products (e.g., whole plant cannabis), and for patients with diverse demographic or clinical characteristics. Recommendations for future research include studies evaluating appropriately representative and diverse populations (including adolescents), studies evaluating specific cannabis-based products available in the United States, studies on long-term outcomes, studies on nonneuropathic chronic pain, studies comparing effects of cannabis-based products versus other treatments for chronic pain, head-to-head studies of different cannabis products, and studies on subacute pain.

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1. Introduction

1.1 Background

Chronic pain, defined as pain lasting longer than 3 to 6 months or past normal time for tissue healing,[13,14] is a serious public health issue in the United States, affecting approximately 100 million people[15] and resulting in over $560 billion annually in costs.[16] Chronic pain substantially impacts physical and mental functioning, reducing productivity and quality of life. It is the leading cause of disability and is often refractory to treatment.[17,18] Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015;[19] although opioid prescribing rates have declined since 2016, they remain substantially higher than pre-1999 levels.[20] The increase in opioid prescribing was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[19,21,22] involving prescription opioids. From 1999 to 2021, approximately 280,000 people died from overdoses related to prescription opioids in the United States, with an estimated 14,716 prescription opioid overdose deaths in 2022.[23] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[24]

While opioids are often prescribed for chronic pain, they are associated with small to moderate effects on pain and overall function and frequent adverse effects.[25] The 2022 Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy as preferred treatment for chronic pain.[26] Recent systematic reviews found that several nonopioid drugs,[27] and some nonpharmacologic treatments,[28] also have small to moderate effects on chronic pain and overall function. Some nonopioid pharmacological treatments had frequent overall adverse events with infrequent serious adverse effects, while nonpharmacological treatments typically reported few adverse events.[27]

The challenges of treating chronic pain, in the context of the limited benefits of commonly prescribed prescription medications and potential harms of opioids, have catalyzed a search for alternative pain treatments, including cannabis. Ideally, alternative treatments would have equal or better benefits for pain compared to opioids, while avoiding potential unintended consequences that could result in harms. Plants have historically been evaluated for medicinal properties, with some being developed into drug therapies (i.e., the field of pharmacognosy). Some preclinical data suggest that cannabinoids may have analgesic properties, though research in this area is mixed.[29] Tetrahydrocannabinol (THC), one of over 140 cannabinoids in cannabis,[30] has demonstrated analgesic properties,[7,8] though its psychoactive and intoxicating effects and the potential for development of use disorder may increase its risk and lessen its suitability as an analgesic. Cannabidiol (CBD), the other primary cannabinoid found in the cannabis plant, may also have anti-inflammatory and analgesic effects and is not thought to be intoxicating or addictive, but may not be as potent as THC.[31,32] Other cannabinoids are present in smaller amounts (e.g., cannabigerol [CBG], cannabinol [CBN], and cannabichromene [CBC]) and may also have some analgesic or anti-inflammatory properties, but are not as well-characterized or studied. Observational studies indicate that some patients use cannabis and related compounds as a substitute for opioids.[33-36]

Other plant-based compounds (PBCs) such as kratom, although pharmacologically distinct from cannabis, may be considered as analgesics, in part due to use in the community as substitutes for opioids.[37,38] They may also have serious harms, such as dependence, addiction, and physiological withdrawal potential.[39] Although some PBCs thought to reduce pain are

currently classified as Schedule I by the Drug Enforcement Administration, there is inconsistency in scheduling others, such as kratom.[40] Recent legalization of cannabis by many states for medical or recreational use[41] may lead to more and higher quality research on PBCs with potential for treating chronic pain.[42] Initiatives to develop and study alternative interventions for chronic pain are expected to contribute to this increase in research on PBCs, specifically for pain. This living review was initiated in response to a request from Congress on PBCs for chronic pain.[42,43]

Although the original review and prior surveillance reports and updates focused on chronic pain in adults, subacute pain as well as the adolescent population are also relevant and subsequently added to the scope of this living review. Subacute pain, often defined as pain lasting for 4 to 12 weeks, represents a transitional state between acute (<4 weeks) pain, which often resolves, and chronic pain, which is more likely to persist.[44] Effective treatments for reducing the likelihood of subacute pain becoming chronic are also needed. Adolescents also experience chronic pain and have a high prevalence of cannabis use (recreational or medical).[45,46]

The key decisional dilemmas for treating chronic pain with cannabis and other PBCs include the effectiveness in treating chronic or subacute pain and the effect of specific formulations, doses or potencies, routes of administration, types of pain, and other patient characteristics on outcomes. It is also important to identify harms of these interventions which may include risks of frequent or daily use, risk of developing cannabis use disorder, mental health effects, and impacts on harms of co-prescribed opioids. It is also unclear what the impact of using cannabis or other PBCs for pain has on opioid use, and, how their effectiveness compares to other interventions.

1.2 Purpose and Scope of the Systematic Review

This is the fourth and final annual update of a "living systematic review" originally addressing the effectiveness and harms of plant-based treatments for chronic pain in adults, now also addressing subacute pain and adolescents. The review was living, meaning that it used methods to identify and synthesize recently published literature and adapt its scope on an ongoing basis. For the purposes of this review, included PBCs were those that have potential analgesic effects as well as the potential for addiction, misuse, and serious adverse effects; other PBCs, such as herbal treatments were not included. The intended audience includes policy and decision makers, funders and researchers of treatments for pain, and clinicians who treat pain.

2. Methods

2.1 Review Approach

This Systematic Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter "AHRQ Methods Guide").[47] All methods were determined a priori, and the original protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/protocol and on the PROSPERO systematic reviews registry (registration no. CRD42021229579).[48] Based on input from a Technical Expert Panel, the protocol was expanded for the 2023 and subsequent updates to include adolescents and subacute pain.[49] Below is a summary of the specific methods used in this review. Search strategies are shown in Appendix A, and detailed methods are presented in Appendix B.

2.2 Key Questions

This review will address the following Key Questions:

1. In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?
2. In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?
3. In adults or adolescents with chronic or subacute pain, what are the benefits of kratom or other plant-based substances for treatment of chronic or subacute pain?
4. In adults or adolescents with chronic or subacute pain, what are the harms of kratom or other plant-based substances for treatment of chronic or subacute pain?

2.3 Study Selection

Electronic searches were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through April 28th, 2025, with automated monthly searches to identify newly published studies. Search strategies were updated for the 2023 review to include terms for subacute pain and applied to databases from inception to identify studies on subacute pain. The original search terms did not exclude adolescents, although previously excluded studies were reassessed for eligibility based on the revised inclusion criteria. The search strategies are shown in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and two prior AHRQ pain reports[25,27] to identify studies that met the inclusion criteria for this review. For the original 2021 review, a Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies. Pre-established criteria were used to determine eligibility for inclusion and exclusion of abstracts in accordance with the AHRQ Methods Guide,

based on the Key Questions and populations, interventions, comparators, outcomes, timing, and settings (PICOTS; Table 1).[47] Following the second annual update, we excluded studies that did not report the specific cannabis products or categories used, due to potential variability in effects for different cannabis products. See Appendix B for more details on eligibility criteria and methods for study selection, including dual review of studies screened.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic (>12 weeks or pain persisting past the time for normal tissue healing) or subacute pain (pain lasting 4 weeks to 3 months). See categorization of specifically included pain populations below.	**All KQs:** Children; adults with acute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4 :** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Nonplant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, general function [e.g., Short-Form 36 Physical Functioning Scale] or pain-related [e.g., Oswestry Disability Index or Roland-Morris Disability Questionnaire, for low back pain] or disability, including pain interference[a]); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder, serious adverse events as defined by study); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

Abbreviations: KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial.

[a] The degree to which pain directly interferes with patients' ability to participate in their daily activities (challenges in performing daily, social, or work-related tasks due to pain).

2.4 Data Extraction and Risk of Bias Assessment

After studies were selected for inclusion, data were abstracted into evidence tables in categories that included but were not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results. Information relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention (including regulatory status and availability in the United States),

and care settings. All study data were abstracted by one team member and verified for accuracy and completeness by a second team member.

The risk of bias of individual studies was assessed using methods consistent with the AHRQ Methods Guide.[47] Separate criteria were used for randomized controlled trials and observational studies. Two reviewers independently assessed risk of bias, resulting in final ratings of low, moderate, or high, with any disagreements resolved by consensus. For full details regarding data extraction, risk of bias assessment, and other methods, please see Appendix B.

2.5 Data Synthesis and Analysis

We constructed summary tables of the abstracted study characteristics, results, and risk of bias ratings for all included studies. Data were additionally summarized in in-text tables, using ranges and descriptive analysis to assist in interpretation of the results. We assessed the persistence of benefits or harms by evaluating the three periods consistent with prior AHRQ pain reports (1 to <6 months, 6 to 12 months, and ≥12 months).[25,27,28,50,51]

Based on input from a Technical Expert Panel regarding potential differences in cannabis products that could impact estimates of benefits and harms, we organized cannabis interventions into three prespecified categories based on their ratios of tetrahydrocannabinol (THC) to cannabidiol (CBD) (Table 2). The first category, high THC, includes products with a ratio of THC to CBD of at least 2 to 1, including products consisting of THC alone. This category was further stratified based on whether interventions were synthetic or plant-derived. Plant-derived products can be extracted with limited purification or undergo additional purification, depending on the process used. We classified un-purified products that were plant-derived as extracted; in addition to THC and CBD, such products may contain additional cannabinoids and other compounds (e.g., terpenes) present in whole-plant cannabis that may or may not affect the impact of the intervention. We classified purified products as pharmaceutical grade products considered free of contaminants and consisting of only a single cannabinoid (i.e., only THC [or THC analogue] or CBD). Although purified dronabinol and CBD are plant derived, they are chemically identical to synthetic dronabinol and CBD.[52] Therefore, we grouped purified with synthetic THC and CBD in primary analyses. However, due to the potential for differential effects of synthetic and purified products, we also performed secondary analyses in which purified dronabinol and CBD were evaluated as a separate category from synthetic dronabinol and CBD.

The second category, low THC, contains a ratio of THC to CBD of less than 1 (i.e., lower THC than CBD, with ratio less than 1 to 2). These may be either extracted or purified products.

The third category, comparable THC to CBD ratios, consists of products with ratios that fall between the other two groups (generally, close to 1 to 1); these may also be extracted or purified products.

Interventions consisting of whole-plant cannabis products (not extracted, purified, or synthetic) were categorized according to information provided about the THC to CBD ratio. Interventions using specific cannabinoids or substances derived from cannabis other than or in addition to THC and CBD were categorized separately.

Within the same THC to CBD category, we analyzed oral and oromucosal (e.g., sublingual or oromucosal spray) or topical products separately from topical products, unless the oromucosal or topical product was clearly designed to produce systemic (rather than local) effects. In such cases, the oromucosal or topical product with systemic effects was analyzed together with oral products.

2. Methods

After our categorization scheme was developed and utilized in the original report and annual updates, the U.S. Food and Drug Administration (FDA) released a document summarizing the research and drug approval process for cannabis. The FDA document categorized cannabis products as "cannabis-derived compounds" occurring naturally in the plant (corresponding to the "plant-derived" category in this report) and "cannabis-related compounds" (corresponding to the "synthetic" category in this report). The FDA document did not describe categories based on THC to CBD ratio or product formulation; in addition, it did not describe separate subcategories of plant-derived products (i.e., extracted and purified). Due to the potential importance of these factors when evaluating cannabis, we elected (in consultation with the Technical Expert Panel) to retain our original categorization scheme.

Table 2. Organizing principle of cannabis-related studies based on ratios of THC to CBD

Intervention Category (Definition)	Source	Possible Derivatives	Example Products	U.S. Availability
High THC (THC to CBD ratio equals ≥2:1 ratio)	Synthetic	Synthetic THC (100% THC or analog)	Dronabinol (Marinol®) or nabilone (Cesamet®)	Available via prescription[a]
	Purified	Purified from whole-plant with close to 100% THC	Purified dronabinol[b,c] (e.g., Namisol®)	Not available in the U.S.
	Extracted	Commercially marketed product extracted from whole-plant with known high ratio of THC/CBD	THC/CBD extracts with high THC/CBD ratio	May be available at dispensaries where allowed
	Extracted	Whole-plant with known high concentration of THC	Whole-plant cannabis with known high THC concentration	May be available at dispensaries where allowed
Comparable THC to CBD (THC to CBD ratio is <2:1 and >1:2)	Extracted	Extracted from whole-plant with comparable ratio of THC/CBD	Nabiximols (Sativex®)[d]	Not available in the U.S.
	Extracted	Extracted from whole-plant with comparable ratio of THC/CBD	Oral tinctures with similar ratio of THC/CBD	May be available at dispensaries where allowed
	Extracted	Whole-plant with known comparable ratio of THC/CBD	Whole-plant with known comparable ratio of THC/CBD	May be available at dispensaries where allowed
Low THC (THC to CBD ratio is ≤1:2)	Synthetic	Synthetic CBD	CBD oral tablets	Not available in the U.S.
	Purified	Purified from whole-plant with close to 100% CBD	Purified CBD	May be available at dispensaries where allowed
	Extracted	Extracted from whole plant with low ratio of THC/CBD; may undergo further purification	CBD topical, sublingual or oral	May be available at dispensaries where allowed
Whole-Plant Cannabis Products (THC to CBD ratio categorized based on information provided [potentially unknown])	Plant-based	Whole-plant products	Cannabis flowers, resins, buds, leaves, hashish	May be available at dispensaries where allowed.
Other Cannabinoids (Cannabinoids other than THC or CBD)	Extracted	Extracted from whole-plant	Cannabidivarin extracted oil (oral)	May be available at dispensaries where allowed
	Plant-based	Derived from hemp seed	Topical hemp seed oil	Available as a food and dietary supplement
	Purified	Purified from whole-plant with close to 100% cannabinol	Topical oil in combination with THC and CBD	Currently does not appear available in the U.S.

Abbreviations: CBD = cannabidiol; FDA = Food and Drug Administration; THC = tetrahydrocannabinol.

[a] These products are approved by the FDA for nonpain indications (anorexia related to HIV infection, nausea related to chemotherapy).
[b] These plant-derived, purified products are chemically identical to dronabinol, and are therefore grouped together with synthetic dronabinol.
[c] Manufactured in the Netherlands and Denmark, may be available in some European countries. Not currently FDA-approved.
[d] Manufactured and available in Canada and some European countries; not FDA-approved.

Meta-analyses were conducted to summarize randomized controlled trial data and obtain more precise estimates on outcomes for which studies were similar enough to provide a meaningful combined estimate.[53] Factors supporting the decision to conduct quantitative synthesis depended on the presence of at least two studies with similar cannabis-related products, methodology, and reported outcomes. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[54] Pain intensity scales were converted to a standardized 0 to 10 scale and the mean difference between groups was used as the effect measure for change in pain. For function or disability, the standardized mean difference (SMD) was used as the effect measure, due to differences in the scales and measures used. For other continuous outcomes, the mean difference on the original scale was used if all studies used the same measure; otherwise, the SMD was used. When the standard deviation for continuous outcomes was not reported or could not be calculated from the reported data, it was imputed using the average coefficient of variation from other included studies. For primary binary outcomes (pain response and adverse events), relative risk was used as the effect measure. See Appendix B for more details regarding meta-analysis methods.

We used a random effects model based on the profile likelihood method[55] to combine interventions with comparable THC to CBD ratios, high-THC trials, and low-THC trials. The primary analysis was stratified by the type of product evaluated. Synthetic and purified products were analyzed together, based on their identical chemical composition, and extracted products were analyzed separately. Sensitivity analysis was conducted by excluding studies rated as high risk of bias and evaluating purified products separately from synthetic products. For meta-analyses with more than 5 but fewer than 20 studies, we also performed sensitivity analyses by repeating analyses using the Bartlett's correction, which can provide improved confidence interval coverage probabilities (i.e., wider confidence intervals) in these situations.[56,57] Meta-analyses were conducted using command *metan* and *admetan* in Stata/SE 16.1 (StataCorp, College Station, TX). Publication bias (small study effect) was assessed using both funnel plots and the Egger test when there were eight or more studies included in a meta-analysis.

The magnitude of effects for primary outcomes were classified according to the same definitions used in other recent AHRQ reviews on chronic pain[25,27,28,50,51] to provide a consistent benchmark for evaluating the relative size of effects of pain interventions across reviews. The magnitude of effect was categorized as small, moderate, or large, based on the criteria shown in Table 3. Results that were below the threshold for a small effect were considered to reflect "no effect" or a trivial effect. Results with a small, medium, or large effect that were not statistically significant were considered to have "potential effects."

Table 3. Definitions of effect sizes

Effect Size	Definition
No effect/trivial effect	• Below the threshold for a small effect
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.
Note: For pain and function, negative values for MD indicate improved outcomes; for other outcomes, positive values indicate improved outcomes.

Small effects in this categorization may be below published thresholds for clinically meaningful effects. However, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients, a small improvement in pain or overall function using a treatment with low cost or no serious harms may be important.

When data were available, we conducted subgroup analysis based on duration (short-, medium-, long-term followup), type of pain (e.g. neuropathic, visceral, joint), and excluding high risk of bias studies.

2.6 Grading the Strength of the Body of Evidence

We assessed the strength of evidence for all primary comparisons and outcomes listed above. The strength of evidence was based on the cumulative evidence (evidence identified for the original report plus new evidence added for the update). Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the AHRQ Methods Guide.[47,58] To ensure consistency and validity of the evaluation, the strength of evidence was reviewed by the entire team of investigators prior to assigning a final grade, based on the following domains:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting/publication bias (suspected or undetected)

For description of the overall grade categories, see Appendix B.

In narratively describing the findings on the strength of the evidence, we followed the principles outlined in recent guidance to improve clarity.[59-61] Using these principles, evidence that is low-strength is described as "may" have an effect, moderate strength evidence is described as "probably" has an effect, and high-strength evidence is described as having an effect.

2.7 Living Systematic Review Methods

This is an annual update of a systematic review originally published in 2021[62] and updated in 2022[63], 2023,[64] and 2024.[65] Quarterly surveillance of the literature conducted prior to this full update and describing new evidence as it is identified can be found at: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review. Due to the relatively small volume of new studies, the quarterly report format was abridged in late 2023. The new abridged format consisted of an updated literature flow diagram, a table of studies included since the 2023 review, and a brief description of whether new studies would impact findings. The availability of new studies likely to significantly impact findings would trigger a more detailed update report.

3. Results

3.1 Description of Included Evidence

The results of this systematic review were organized first by Key Questions, with evidence on Key Questions 1 and 2 (benefits and harms of cannabinoids) reported together. The evidence was then organized according to the categories described in the Methods, comparable tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio extracted interventions, high THC to CBD ratio interventions (synthetic, purified, or extracted), low THC to CBD ratio interventions (synthetic, purified, or extracted), and other cannabinoids. No eligible studies were identified for the Key Questions examining kratom (Key Questions 3 and 4). No studies addressed subacute pain or adolescents.

For this update, three new RCTs[1-3] and three new observational studies[4-6] were identified. Two new RCTs were placebo-controlled: one evaluated plant-derived topical hemp seed oil or diclofenac 1% gel for knee osteoarthritis[1] and one evaluated purified topical THC:CBD:cannabinol (CBN) in a 3.20:0.32:0.65 ratio for diabetic neuropathy.[2] The cannabis products evaluated in both new placebo-controlled RCTs represented new product types for this review. Hemp seed oil primarily consists of polyunsaturated fatty acids; it does not contain THC and has only trace amounts of CBD. CBN is a THC metabolite/oxidative byproduct that is mildly psychoactive and may have analgesic and anti-inflammatory effects. Due to the inclusion of CBN and the topical mode of administration, this product was considered separately from the oral or sublingual high THC to CBD ratio products previously included in the living review. The third new RCT compared purified inhaled cannabis in a comparable (6.3% THC and 8% CBD) THC to CBD ratio, 5 mg oxycodone tablets, or both for fibromyalgia.[3] The three new observational studies (n=741, 96 and148)[4-6] included patients with various chronic pain conditions and evaluated various low, comparable, or high THC to CBD ratio cannabis products.

The search results and selection of studies are summarized in the literature flow diagram (Figure 1). Appendix C provides a list of all included studies. Seven placebo-controlled RCTs evaluated products that contain a combination of extracted THC and CBD in a comparable ratio,[66-72] and one new, head-to-head RCT evaluated a product that contained a a combination of purified THC and CBD in a comparable ratio versus oxycodone or both.[3] Two RCTs evaluated the effects of extracted high THC to CBD ratio products.[73,74] Eleven placebo-controlled RCTs evaluated synthetic or purified THC (high THC to CBD ratio).[75-85] Seven placebo-controlled RCTs evaluated low THC to CBD ratio products.[84-90] Six of these evaluated CBD alone: three RCTs evaluated synthetic oral CBD;[84,85,88] one RCT evaluated topical intraoral CBD (unclear if synthetic or plant-derived);[90] one RCT evaluated purified oral CBD;[87] and one RCT evaluated extracted topical CBD.[89] Two of the RCTs of oral synthetic CBD also evaluated the combination of purified THC plus synthetic CBD (1:2 ratio)[84,85] and one RCT assessed extracted sublingual THC/CBD oil [1:6 ratio].[86] Three placebo-controlled RCTs evaluated "other" cannabis-based products. One RCT evaluated the phytocannabinoid cannabidivarin (CBDV), administered as an oral oil;[91] one new RCT evaluated purified topical THC:CBD:CBN (cannabinol) oil in a 3.20:0.32:0.65 ratio;[2] and one new RCT evaluated a hemp seed oil.[1] Seven RCTs reported prior cannabis use in 3 to 47 percent of participants[66,68-71,88,89] and two RCTs reported cannabis use in the past year in 6 and 10 percent of participants.[67,72] Ten RCTs excluded patients with any cannabis use or recent cannabis use (and did not report the proportion of patients with any prior use),[3,74-76,79-82,86,91] and nine RCTs did not report prior cannabis use.[1,2,73,77,78,83-85,87]

3.1 Results, description of included evidence

Appendix D summarizes key outcomes from each RCT and results of meta-analyses. Detailed evidence tables for included studies and risk of bias assessments are available in Appendixes E and F. Appendix G contains details on the strength of evidence, and Appendix H lists excluded studies at the full-text level and their reasons for exclusion.

Figure 1. Literature flow diagram

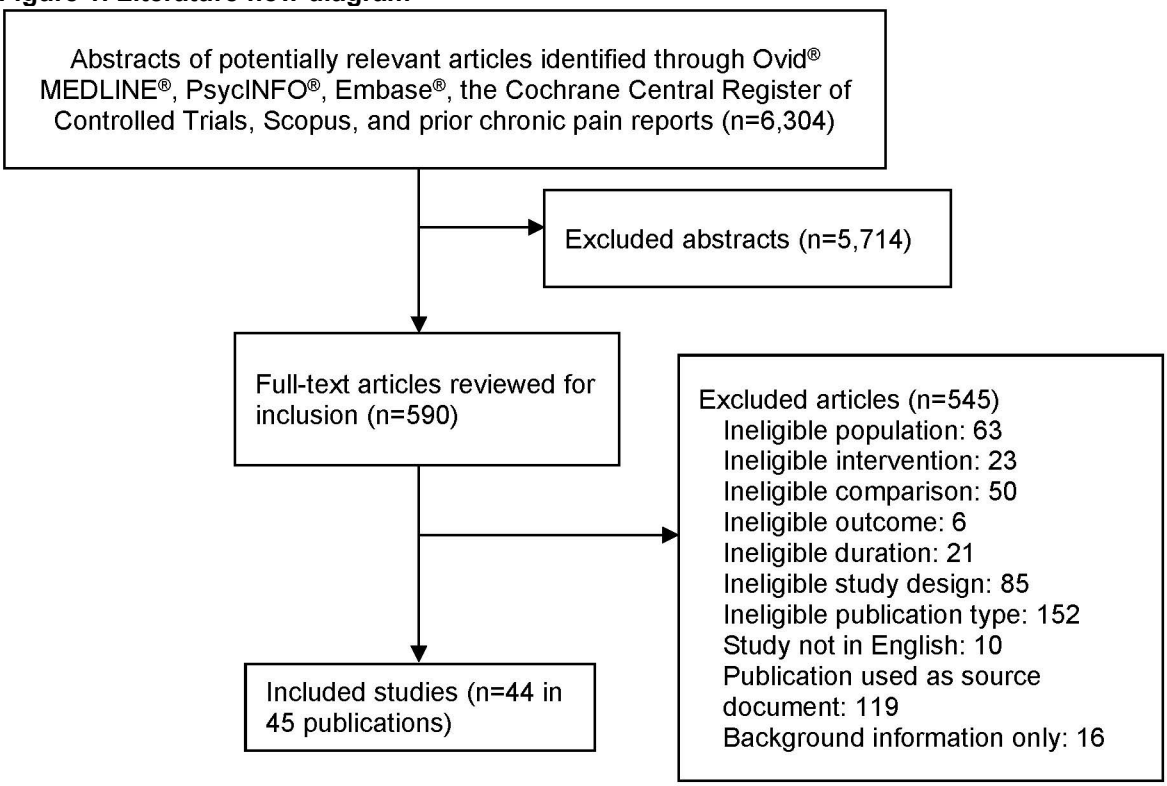

Abstracts of potentially relevant articles identified through Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Central Register of Controlled Trials, Scopus, and prior chronic pain reports (n=6,304)
Excluded abstracts (n=5,714)
Full-text articles reviewed for inclusion (n=590)
Excluded articles (n=545)
Ineligible population: 63
Ineligible intervention: 23
Ineligible comparison: 50
Ineligible outcome: 6
Ineligible duration: 21
Ineligible study design: 85
Ineligible publication type: 152
Study not in English: 10
Publication used as source document: 119
Background information only: 16
Included studies (n=44 in 45 publications)

Table 4 summarizes the characteristics of the included trials, and Table 5 provides details on included observational studies.

Table 4. Characteristics of included randomized controlled trials of cannabinoids for chronic pain in adults

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
THC to CBD Ratio	Comparable[a]	High	Low	NA - other cannabinoids
Source	Extracted Purified	Synthetic Purified Extracted	Synthetic Purified Extracted Unclear	Extracted Purified
N Studies	8 (1 new)[b]	13	7 (1 topical, 1 sublingual, 4 oral, 1 unclear)	3 (2 new)[b]

3.1 Results, description of included evidence

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
Comparator (Study Count)	Placebo (7); 5 mg oxycodone or a combination of 5 mg oxycodone and inhaled cannabis (1)	Placebo (10); Ibuprofen (1); Diphenhydramine (1); Dihydrocodeine (1); Low THC to CBD ratio (CBD or purified THC/CBD) (2)	Placebo (7); Dronabinol (2); Low THC to CBD ratio (CBD or purified THC/CBD (2); ≥97% purified low THC to CBD (1:6) sublingual oil (1); 5% or 10% CBD gel (unclear if synthetic or plant-based) (1)	Placebo (3); diclofenac 1% gel (1)
Route of Administration, Formulation (Study Count)	Sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl (7); Purified cannabis capsules inhaled using a vaporizer, 150 mg per capsule (1)	Dronabinol 3 mg oral tablet (1); Dronabinol 2.5 mg oral capsule (1); Dronabinol 5 mg oral capsule (1); Nabilone oral 0.25 mg capsule (1); Nabilone oral 0.5 mg capsule (5); Purified dronabinol oral 2.5 mg capsule (2); Oral capsule, 2.5 mg purified THC/0.8 – 1.8 mg CBD extract (1); Sublingual oil drops, 24 mg/ml THC/0.51 mg/ml CBD (1)	Oral capsule, 5 mg synthetic CBD (2); Oral tablet, 10 mg synthetic CBD (1); Oral capsule, 200 mg purified CBD (1); Oral capsule, 5 mg CBD extract/2.5 mg dronabinol (2); Sublingual oil, 24.5 mg/mL THC, 147 mg/mL CBD (1); Topical cream, 83 mg CBD/fluid ounce (1) 5% or 10% CBD gel, unclear if local or systemic (1)	Oral oil, 50 mg/ml CBDV (1); Topical hemp seed oil, concentration NR (1); Topical THC:CBD:CBN oil in a 3.25:0.32:0.65 ratio (1)

3.1 Results, description of included evidence

Characteristic	THC/CBD	THC	CBD	Other Cannabinoids
Dosing Regimen	Oromucosal spray: Final mean dose 23 mg THC/21 mg CBD daily Inhaled cannabis: Maximum of three 150 mg capsules per day in week 1, increasing up to five capsules	Dronabinol capsules: 2.5 to 5 mg, titrated. Final dose range 13 - 25 mg/day Dronabinol (Namisol®[a]) tablet: 3 to 8 mg 3 times daily, titrated. Final dose NR Nabilone 0.25 - 2 mg twice daily, titrated. Final mean dose 1.84 Capsule: 2.5 -12.5 mg THC twice daily, titrated. Final dose NR Oral oil: 1.2 mg daily Sublingual drops: 1.2 mg daily, titrated. Final dose 4.4 mg THC daily	Oral CBD capsule: 5 mg twice daily, titrated. Final median dose 45 to 50 mg CBD daily (2) Oral tablet: 10 mg daily, titrated (max 3 times daily) Final dose NR Oral CBD capsule: 200 mg 3 times daily. Final dose 600 mg/day Oral dronabinol/CBD capsule: 2.5 mg THC/5 mg CBD twice daily, titrated. Final median dose 12.5 to 15 mg THC/30 to 45 mg CBD daily (2) Sublingual oil, titrated to max daily dose of 6 drops 3 times daily (15 mg THC/90 mg CBD) Topical cream: applied locally 1-4 times/day (volume/dose, final dose NR) CBD gel: 20 mg of 5% or 10% gel applied on each side, total dose 20-40 mg daily	400 mg CBDV daily. Final dose NR Topical hemp seed oil: 10 drops daily (dose NR) THC:CBD:CBN oil: 1-2 drops for mild pain; 3-4 drops for for moderate pain; 5-6 drops for severe pain
Risk of Bias	25% high, 63% moderate, 12% low	8% high, 46% moderate, 46% low	43% high, 43% moderate, 14% low	100% moderate
Total Randomized	963	1,028	568	224
Age, Mean Years	53	54	54	57
Female, %	71%	62%	60%	51%
Non-White,[c] %	1.6% (2)	5.3% (4)	NR	NR
Primary Pain Type (Study Count)	NPP (6); Inflammatory arthritis (1); Fibromyalgia (1)	NPP (9); Fibromyalgia (2); Visceral pain (1); Headache (1);	NPP (3); MS (1); OA (2); Temporomandibular (1); Unspecified (1)	NPP (2), OA (1)
Baseline Pain Score, Mean (Range)[d]	6.89 (6.4 to 7.30)	6.75 (4.00 to 8.67)[e]	6.01 (4.67 to 7.40)[f]	4.77 (2.54 to 6.28)
Study Duration	4 to 15 weeks	4 to 47 weeks	4 to 16 weeks	4 to 12 weeks

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; CBN = cannabinol; MS = multiple sclerosis; NA = not applicable; NPP = neuropathic pain; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; THC = tetrahydrocannabinol.

[a] All products were nabiximols.

[b] Two trials are included in both the THC and CBD columns, as they compared THC to CBD, CBD/THC, and placebo.

[c] (n) = number of studies reporting this characteristic at baseline.

[d] Scores were standardized to a 0 to 10 scale.

[e] Mean pain score includes median scores for 1 study (6 vs. 6).

[f] Mean pain score includes median scores for 1 study (5.2 vs. 6.1).

Note: Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

3.1 Results, description of included evidence

Table 5. Characteristics of included observational studies of cannabinoids for chronic pain in adults

Characteristic	THC/CBD[a]	THC	Synthetic THC	THC/CBD Versus Synthetic THC	THC/CBD Versus LAOs
THC to CBD Ratio	Unclear, mixed, or various	High	High	Comparable vs. high	Comparable
Source	Any cannabis product (patient's choice) or mixed cannabinoids	Extracted	Synthetic (nabilone)	Extracted vs. synthetic	Extracted
N Studies	11 (3 new)[b]	1	1	1	1
Comparator (Study Count)	No cannabis use (3); usual care (1); no medical cannabis authorization (2); other cannabinoids (5)	Usual care (1)	Gabapentin only; gabapentin + nabilone (1)	Active comparator; oral mucosal spray vs. dronabinol	Long-acting opioids (MME 69.4 [SD 38.9] mg/day)
Route of Administration, Formulation	Unreported (any available allowed, patient's choice) (6); inhaled or oral prescribed cannabis (5)	Whole-plant cannabis, "certified 12.5% THC" (CBD NR) route determined by patient: smoking 27%, oral 8%, vaporization 4%, combination 61%	Nabilone 0.5 mg oral capsule	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Dronabinol oral capsule (strength NR)	Nabiximols sublingual oromucosal spray, 2.7 mg THC/2.5 mg CBD per 100 mcl Oral long-acting opioids (dose varied)
Dosing Regimen	None specified (9) Final median dose 85 mg CBD vs. 7.8/20 mg THC/CBD vs. 20/25 mg THC/CBD vs. 42 mg THC/day (1) Final median dose of 25 mg THC and 20 mg CBD (1)	None specified; titrated to max dose 5 g/day. Final median dose 2.5 g/day	None specified; final mean dose 3 mg/day	None specified; final mean dose 16.6/15.4 mg THC/CBD/day vs. 17.2 mg THC/day	None specified; based on individual patient needs; final mean dose 16.7/15.5 mg THC/CBD/day vs. MME 69.4 mg/day
ROB	55% high, 45% moderate	100% high	100% moderate	100% moderate	100% moderate
N Total	47,179	431	156	674	1,310
Age, Mean Years	52	49	61	46	51
Female, %	56%	57%	59%	57%	57%
% Non-White (Study Count)	54% (1); NR (10)	NR	NR	NR	NR
Primary Pain Type(s)	Mixed musculoskeletal, chronic noncancer pain (10) Fibromyalgia (1)	Chronic noncancer pain	NPP	Peripheral NPP	Peripheral neuropathic back pain
Baseline Pain Score, Mean (Range)[c]	5.90 (4.60 to 7.47)[d]	6.35 (6.1 to 6.6)	4.98 (4.58 to 5.31)	4.4 (4.39 to 4.41)	4.32 (4.31 to 4.33)
Study Duration, Weeks (Range)	12 to 208	52	26	24	24

Abbreviations: CBD = cannabidiol; LAO = long acting opioid; MME = morphine milligram equivalents; NPP = neuropathic pain; NR = not reported; ROB = risk of bias; SD = standard deviation; THC = tetrahydrocannabinol.

[a] Patients could choose any medicinal product they preferred in these studies.

[b] Includes three new studies for this review.

[c] Scores were standardized to a 0 to 10 scale.

[d] Mean includes median scores for 2 studies

Note: Text that is red indicates that a new study has been added. Color is used for visual emphasis only.

3.2 Key Question 1 and Key Question 2. In adults or adolescents with chronic or subacute pain, what are the benefits (Key Question 1) and harms (Key Question 2) of cannabinoids for treatment of chronic or subacute pain?

3.2.1 Key Points for Comparable THC to CBD Ratio

- All results are short term (4 weeks to <6 months) in duration.
- Comparable extracted THC to CBD ratio oromucosal spray was associated with small improvements in pain severity (7 RCTs, N=878, 0 to 10 scale, mean difference [MD] −0.54, 95% confidence interval [CI], −0.95 to −0.19, I^2=39%) versus placebo (strength of evidence [SOE]: moderate), and effects on function that were just below the threshold for a small improvement (6 RCTs, N=616, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16, I^2=32%) versus placebo (SOE: moderate). While more patients experienced a pain response (≥30% improvement from baseline), fewer trials reported this outcome and the difference was small and did not reach statistical significance (4 RCTs, N=733, 38% vs. 31%, relative risk [RR] 1.18, 95% CI 0.93 to 1.71, I^2=36%) (SOE: low).
- Compared with placebo, comparable extracted THC to CBD oromucosal spray was associated with a large increase in risk of dizziness (6 RCTs, N=866, 31.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%) (SOE: low) and sedation (6 RCTs, N=866, 8.0% vs. 1.2%, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%) (SOE: low), and a moderate increased risk of nausea (6 RCTs, N=866, 14% vs. 7.5%, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%) (SOE: low). There was no effect on study withdrawal due to adverse events (WAEs) (SOE: low).
- One new, head-to-head RCT (n=81) of a purified, comparable ratio inhaled THC to CBD product versus oxycodone or a combination of both found no differences in median pain score or likelihood of experiencing at least 1 point reduction in pain score (0 to 10 scale). Function was not reported and reporting of adverse events was suboptimal.

3.2.2 Summary of Findings for Comparable THC to CBD Ratio

Seven RCTs (N=882, range 18 to 339)[66-72] included in prior updates compared extracted THC and CBD in a comparable THC to CBD ratio versus placebo in patients experiencing chronic pain. All used nabiximols, which are extracted from whole-plant cannabis with 2.7 mg of THC and 2.5 mg of CBD per 100 mcl oromucosal spray (specified as the product Sativex® in 7 studies). Sativex® is manufactured and available in Canada and some European countries, but not approved by the U.S. Food and Drug Administration (FDA). Other comparable THC to CBD products are available in the United States where allowed, though the availability of specific products is unknown or variable. Six trials enrolled patients with neuropathic pain[67-72] and one trial included patients with rheumatoid arthritis.[66] Studies ranged from 4 to 15 weeks in duration of active treatment; all were limited to short-term followup (1 to <6 months). Across trials, the weighted mean daily dose was 8.4 sprays (23 mg THC/21 mg CBD) for patients assigned to THC/CBD and 12.7 sprays for those assigned to placebo. One study did not specify the product name, strength or dosing in milligrams, but the number of sprays per day (8 vs. 11 for intervention vs. placebo), were similar to other trials.[68] Two trials were high risk of bias: one was

a small (n=16), 4-week, crossover trial, and the other was a small (n=29), 12-week, parallel design trial.[68,71] The rest were parallel design trials; four were rated moderate risk of bias[66,69,70,72] and one low risk of bias.[67] One trial used an enriched enrollment randomized withdrawal design.[67] The mean age of participants in the trials was 53 years, and 62 percent were female. Race was poorly reported, with two trials reporting 1.2 percent of participants being non-White, and the others not reporting race or ethnicity. Four trials allowed patients using opioids and other analgesics to enroll and to continue using them during the study period.[67-69,72] The proportion of patients taking opioids was low in two studies (11% to 24%)[67,72] and much higher in the third study (63% in the cannabis group vs. 74% in the placebo group).[69] The other three trials did not report baseline opioid use. All placebo-controlled RCTs of comparable THC to CBD ratio products allowed prior cannabis use; the proportion of patients that used cannabis previously ranged from 5 to 64 percent. No study analyzed results according to prior cannabis use.

Study details and results are shown in Appendix E, Tables E-1 to E-5, and risk of bias assessments in Appendix F, Tables F-1 and F-2.

Placebo-controlled trials of comparable THC to CBD ratio products. Four RCTs[67,69,71,72] found comparable extracted THC/CBD oromucosal spray (nabiximols) associated with a nonstatistically significant increased likelihood of pain response (≥30% reduction in pain) versus placebo (38% vs. 31%, RR 1.18, 95% CI 0.93 to 1.71, I^2=36%; Appendix D, Figure D-1). Based on pooled analysis of all seven RCTs, comparable THC/CBD was associated with a small, statistically significant reduction in pain severity versus placebo (7 RCTs, 0 to 10 scale, MD −0.54, 95% CI −0.95 to −0.19, I^2=39%; Figure 2).[66-72] Figure 2 shows that, except for a small, high risk of bias, crossover study, the effect size was larger and statistically significant in shorter studies (4 to 5 weeks) compared with longer studies (12 to 15 weeks); however, all studies met the definition for short duration (1 to <6 months). Sensitivity analysis excluding two high risk of bias studies[68,71] did not alter the findings (0 to 10 scale, MD −0.63, 95% CI −1.15 to −0.24, I^2=52%).[67,72] One trial that used an enriched enrollment randomized withdrawal design reported worse results for comparable THC/CBD compared with the pooled estimate (MD −0.19, 95% CI −0.67 to 0.29).[67]

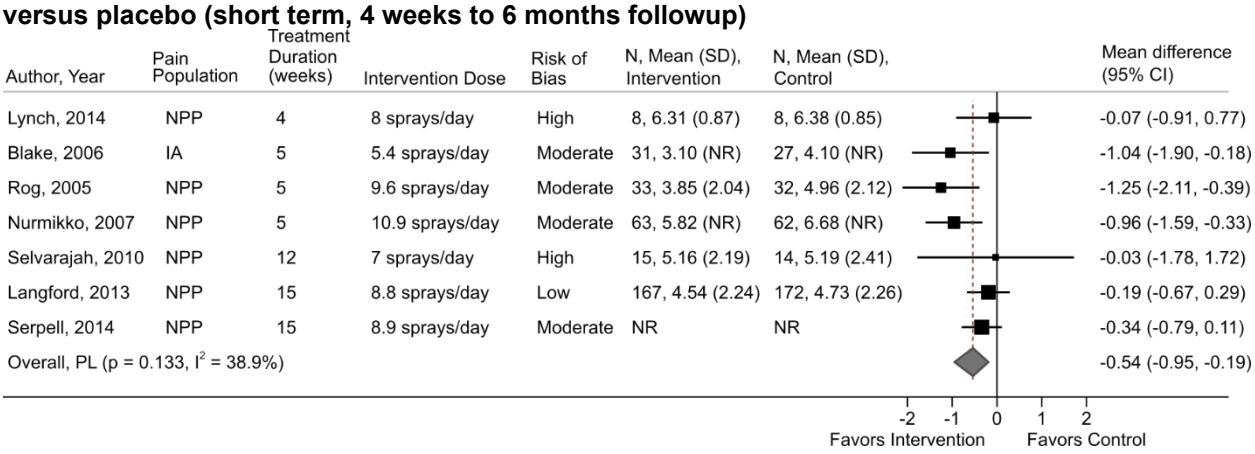
Six studies (N=616) with 5 to 15 weeks followup reported overall function or disability (including measures of pain interference).[66,67,69-72] Pooled analysis favored nabiximols versus placebo, but the difference was slightly below the threshold for a small effect (negative values indicate improved function; 6 RCTs, 0 to 10 scale, MD −0.42, 95% CI –0.73 to −0.16, I^2=32%; Figure 3).

For secondary outcomes, all of the trials reported quality of life. Overall, there were no statistically significant differences in quality of life between nabiximols versus placebo. Three trials used the EuroQol-5 Dimension (EQ-5D) scale (0 to 100), with none finding a significant difference between groups.[67,71,72] One trial used the Short General Health Questionnaire (GHQ-12; 0 to 36 scale), and found a small but nonstatistically significant difference between groups.[69] Three trials reported the Short Form-36 (SF-36) Physical and Mental scales (0 to 100).[67,68,71] Two did not find statistically significant between-group differences. The third study, a high risk of bias crossover trial (n=16), reported that the SF-36 Physical Component Scale scores improved with placebo, with little change in the THC/CBD group, while the SF-36 Mental Component Scale scores remained similar in the THC/CBD group and decreased (worsened) in the placebo group.[68] Five RCTs assessed sleep quality or sleep disturbance using a 0 to 10 scale

and four reported statistically significantly better sleep disturbances scores with THC/CBD versus placebo groups.[66,67,69,70,72] The studies did not report on other secondary outcomes such as depression or anxiety.

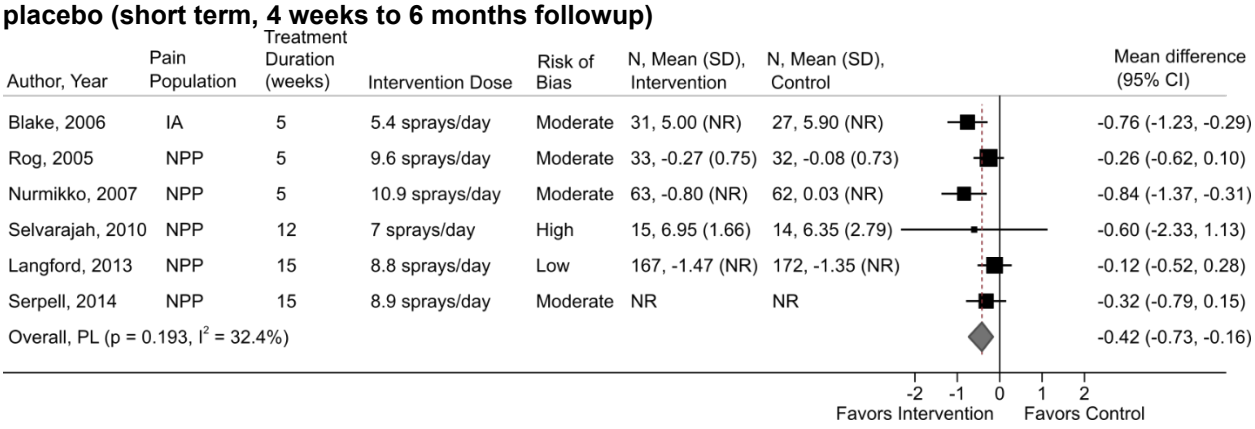
The four RCTs that allowed opioid use did not report on changes in opioid used during the study period.[67-69,72]

Figure 2. Change in pain severity with extracted, comparable THC to CBD ratio oromucosal spray versus placebo (short term, 4 weeks to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean difference (95% CI)
Lynch, 2014 NPP 4 8 sprays/day High 8, 6.31 (0.87) 8, 6.38 (0.85) -0.07 (-0.91, 0.77)
Blake, 2006 IA 5 5.4 sprays/day Moderate 31, 3.10 (NR) 27, 4.10 (NR) -1.04 (-1.90, -0.18)
Rog, 2005 NPP 5 9.6 sprays/day Moderate 33, 3.85 (2.04) 32, 4.96 (2.12) -1.25 (-2.11, -0.39)
Nurmikko, 2007 NPP 5 10.9 sprays/day Moderate 63, 5.82 (NR) 62, 6.68 (NR) -0.96 (-1.59, -0.33)
Selvarajah, 2010 NPP 12 7 sprays/day High 15, 5.16 (2.19) 14, 5.19 (2.41) -0.03 (-1.78, 1.72)
Langford, 2013 NPP 15 8.8 sprays/day Low 167, 4.54 (2.24) 172, 4.73 (2.26) -0.19 (-0.67, 0.29)
Serpell, 2014 NPP 15 8.9 sprays/day Moderate NR NR -0.34 (-0.79, 0.11)
Overall, PL (p = 0.133, I² = 38.9%) -0.54 (-0.95, -0.19)
-2 -1 0 1 2
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol.

Figure 3. Overall function: extracted, comparable THC to CBD ratio oromucosal spray versus placebo (short term, 4 weeks to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean difference (95% CI)
Blake, 2006 IA 5 5.4 sprays/day Moderate 31, 5.00 (NR) 27, 5.90 (NR) -0.76 (-1.23, -0.29)
Rog, 2005 NPP 5 9.6 sprays/day Moderate 33, -0.27 (0.75) 32, -0.08 (0.73) -0.26 (-0.62, 0.10)
Nurmikko, 2007 NPP 5 10.9 sprays/day Moderate 63, -0.80 (NR) 62, 0.03 (NR) -0.84 (-1.37, -0.31)
Selvarajah, 2010 NPP 12 7 sprays/day High 15, 6.95 (1.66) 14, 6.35 (2.79) -0.60 (-2.33, 1.13)
Langford, 2013 NPP 15 8.8 sprays/day Low 167, -1.47 (NR) 172, -1.35 (NR) -0.12 (-0.52, 0.28)
Serpell, 2014 NPP 15 8.9 sprays/day Moderate NR NR -0.32 (-0.79, 0.15)
Overall, PL (p = 0.193, I² = 32.4%) -0.42 (-0.73, -0.16)
-2 -1 0 1 2
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol.

Adverse events were reported in all trials. Based on two RCTs, rates of any adverse event were significantly higher in the THC/CBD groups than placebo (2 RCTs, 75% vs. 63%, RR 1.19, 95% CI 1.02 to 1.44, I^2=0%, Appendix D, Figure D-2).[67,70]

Serious adverse events (SAEs) were reported in five trials, with two reporting that none occurred.[68,70] Pooling results from the other three studies found comparable THC/CBD products and placebo associated with similar risk of SAEs (3 RCTs, 5.0% vs. 4.3%, RR 1.18, 95% CI 0.26 to 3.4, I^2=0%, Appendix D, Figure D-3).[66,69,72]

3.2.3 Results, Key Question 1 and Key Question 2. Benefits and harms of cannabinoids for treatment of chronic or subacute pain, key points for high THC to CBD ratio

Five RCTs reported on study WAEs. There was no difference between extracted comparable THC to CBD ratio products versus placebo in risk of WAEs, though the estimate was imprecise (5 RCTs, 12.3% vs. 9.5%, RR 1.14, 95% CI 0.65 to 3.02, I^2=51%, Appendix D, Figure D-4).[66,67,69,70,72]

Statistically significant differences in specific adverse events occurred more often in the THC/CBD groups than placebo across six RCTs (one did not report specific adverse events).[71] Dizziness occurred significantly more frequently in the THC/CBD groups than placebo groups (6 RCTs, 31.0% vs. 8.0%, RR 3.57, 95% CI 2.42 to 5.60, I^2=0%, Appendix D, Figure D-5).[66-70,72] Nausea was reported in 14 percent of THC/CBD patients compared with 7.5 percent of placebo patients (6 RCTs, RR 1.79, 95% CI 1.19 to 2.77, I^2=0%, Appendix D, Figure D-6).[66-70,72] Sedation was reported in 8 percent of THC/CBD patients compared with 1.2 percent of placebo patients (6 RCTS, RR 5.04, 95% CI 2.10 to 11.89, I^2=0%, Appendix D, Figure D-7).[66-70,72]

A previously included retrospective cohort study (n=1,310) provided insufficient evidence to compare outcomes of nabiximols oromucosal spray (plant-based extracted comparable THC to CBD ratio product) versus long-acting opioids when administered as add-on therapy in patients with neuropathic pain, due to methodological limitations.[92]

Head-to-head trials of comparable THC to CBD ratio products. One new RCT (n=81) compared purified, inhaled (vaporized) THC and CBD (up to 150 mg/day) in a comparable ratio (6.3%:8%, or ~1:1.3) versus oxycodone 5 mg tablets (up to 20 mg/day) or both in patients with fibromyalgia.[3] Median oxycodone use was 3 tablets in the oxycodone only group and 2 tablets in the combined group. Opioid use was otherwise not permitted and patients who used opioids before the trial were tapered off prior to entering. The mean age of participants was 43 years and 98% were female; patients with prior cannabis use were excluded. The trial was rated moderate risk of bias. Methodological shortcomings included unclear randomization and allocation concealment schemes, no masking, and no placebo arm. The trial reported no differences between groups in median pain scores or likelihood of experiencing a decrease of 1 or more points (0 to 10 points) in pain score (data not provided). Function was not reported and reporting of adverse events was suboptimal; it was not possible to determine the proportion of patients in each group experiencing adverse events.

3.2.3 Key Points for High THC to CBD Ratio

- All RCT results were short term (4 weeks to <6 months) in duration.
- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with a small improvement in pain severity (8 RCTs, N=507, 0 to 10 scale, MD −0.78, 95% CI −1.59 to −0.08, I^2=64%) (SOE: low) and no effect on overall function or disability (3 RCTs, N=unclear, 0 to 10 scale, MD −0.18, 95% CI −1.25 to 0.77, I^2=51%) versus placebo (SOE: low).
- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with a moderate increase in risk of study WAEs (6 RCTs, N=487, 14% vs. 7%, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%) (SOE: low), moderate increase in risk of sedation (5 RCTs, N=458, 24% vs. 16%, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%) (SOE: low), a large increase in risk of dizziness (4 RCTs, N=425, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%) (SOE: moderate), and a large increase in risk of nausea (4 RCTs, N=425, 12% vs. 6%, RR 2.12, 95% CI

1.09 to 3.96, I^2=0%) versus placebo, but the differences did not reach statistical significance (SOE: low).

- Synthetic or purified high THC to CBD ratio (100% THC or THC analogue) products were associated with inconsistent effects on likelihood of experiencing a pain response (≥30% improvement) versus placebo (3 RCTs) (SOE: insufficient).
- Extracted high THC to CBD ratio products (not 100% THC) were associated with a large increased risk of study WAEs (1 RCT, N=277, 13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) (SOE: low) and dizziness (1 RCT, N=277, 62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) versus placebo (SOE: low). Outcomes assessing benefit were not reported or evidence was insufficient.
- A combined analysis of synthetic or purified and extracted high THC to CBD ratio products indicated a small improvement in pain severity versus placebo (10 RCTs, N=801, −0.98, 95% CI −1.80 to −0.32, I^2=68%) (SOE: moderate).

3.2.4 Summary of Findings for High THC to CBD Ratio

A total of 13 previously included RCTs evaluated high THC to CBD ratio products.[73-85] Eleven evaluated synthetic THC (dronabinol, 2 RCTs),[78,79] a synthetic THC analog (nabilone, 6 RCTs),[76,77,80-83] or purified dronabinol (3 RCTs).[75,84,85] Two other RCTs evaluated extracted products with both THC and CBD (THC to CBD ratio 48:1 in one study and 2:1 in the other).[73,74] Synthetic dronabinol and nabilone are available by prescription and approved by the FDA for nonpain indications. The availability of purified dronabinol in the United States is unclear, although it is manufactured in the Netherlands and Denmark and may be available in some European countries. Other extracted and high THC whole-plant products are available in the United States, where allowed, though the availability of specific products is unclear or variable.

Seven of the included trials of synthetic or purified RCTs were placebo-controlled,[75,79-85] and three were active-controlled crossover trials.[76-78] One trial of purified THC included both a placebo arm as well as active comparisons against low THC to CBD ratio products.[84] Both trials of extracted THC were placebo-controlled. All of the RCTs were short duration (4 weeks to 6 months followup). Additionally, there were two short duration observational studies,[93,94] one[94] comparing a synthetic THC versus extracted comparable THC to CBD ratio product.

3.2.4.1 Synthetic or Purified THC

Eleven RCTs (N=659; 5 dronabinol, 6 nabilone)[75-85] evaluated synthetic or purified THC for treating chronic pain. Eight trials enrolled patients with neuropathic pain (4 multiple sclerosis [MS], 2 mixed neuropathic pain conditions, and 1 each painful diabetic neuropathy and spinal cord injury),[76,78,79,81-84] and one trial each enrolled patients with chronic abdominal pain,[75] medication overuse headache,[77] and fibromyalgia.[80] All studies had short duration of treatment, ranging from 4 to 14 weeks. All medication doses were titrated upward, with a maximum dose of 15 to 25 mg per day of dronabinol, and 0.5 to 2 mg per day of nabilone. The mean final dose was inconsistently reported.

One trial of nabilone used an enriched enrollment randomized withdrawal design, with a 4-week, single-blind, flexible dose run-in nabilone period prior to randomization.[81] Only patients who achieved a 30 percent improvement in pain severity, completed 75 percent of diary entries, and did not withdraw from the study due to adverse events were randomized to continue

treatment or placebo (discontinuation of nabilone). Thirty percent of patients (11/37) withdrew during the run-in period.

Seven trials used a parallel design and were placebo-controlled, with one adding nabilone or placebo to gabapentin treatment in patients who had not achieved pain relief (defined as visual analog scale [VAS] score for pain >50).[82] Three RCTs were crossover trials with different active controls: diphenhydramine,[78] ibuprofen,[77] and dihydrocodeine.[76] One placebo-controlled RCT also included two low THC to CBD ratio product arms (CBD alone or the combination of THC and CBD in a ratio of ~1:2).[84] Risk of bias was high in two trials,[78,83] moderate in four trials,[75,76,80,82] and low in five trials.[77,79,81,84,85] Across trials, the mean age of participants was 54 years, and 60 percent were female. Race was poorly reported; three trials that described race reported that 5.4 percent of participants were non-White. Three studies allowed patients to continue taking their current medication for pain, not specifically excluding opioids or requiring opioid discontinuation,[75,79,80] with one RCT specifically allowing tramadol as rescue medication for acute pain during the trial.[79] The other studies required patients to discontinue opioid use[76,78,85] or did not report opioid use at baseline or during the study.[77,81-83] Six parallel design placebo-controlled trials (3 dronabinol, 3 nabilone) excluded patients with prior cannabis use.[75,79-82,84] One head-to-head crossover trial (nabilone vs. dihydrocodeine) excluded patients with prior cannabis use.[76]

A previously included, a small (n=156), moderate risk of bias cohort study evaluated nabilone and gabapentin in patients with neuropathic pain of various types for 6 months.[93]

Study details and results are shown in Appendix E, Tables E-1 to E-5, and risk of bias assessments are shown in Appendix F, Tables F-1 and F-2.

Placebo-controlled trials of synthetic and purified THC. Based on a pooled analysis of eight RCTs, synthetic and purified high THC to CBD ratio products were associated with a small improvement in pain severity versus placebo (8 RCTs, N=507, 0 to 10 scale, MD –0.78, 95% CI –1.59 to –0.08, I^2=64%; Figure 4).[75,79-85] However, statistical heterogeneity was present. The estimate was similar to the prior pooled estimate (MD –0.95, 95% CI –1.81 to –0.25, I^2=60%). Results were similar when the analysis was restricted to trials of patients with neuropathic pain (7 RCTs, MD –0.77, 95% CI –1.67 to 0.00, I^2=70%). However, statistical heterogeneity remained present. Excluding the small (n=26), enriched enrollment randomized withdrawal trial[81] also resulted in a similar pooled estimate and did not resolve statistical heterogeneity. Stratified analysis indicated that the pooled effect estimate for nabilone (MD −1.59, 95% CI −2.49 to −0.82, I^2=0%) was larger than with dronabinol (MD −0.23, 95% CI −0.82 to 0.54, I^2=45%; Appendix D, Figure D-8, Table D-6); this difference was statistically significant (p=0.027).[75,79-85] Analyzing purified THC as a separate category from synthetic THC did not resolve statistical heterogeneity among the high THC trials, although results suggested discordant effects for synthetic (moderate benefit, 5 RCTs, MD −1.20, 95% CI −2.21 to −0.47, I^2=58%) and purified products (no benefit, 3 RCTs, MD 0.10, 95% CI −1.08 to 1.02, I^2=48%; Appendix D, Figure D-9).

Three trials reported likelihood of pain response (≥30% improvement from baseline) for synthetic or purified high THC to CBD ratio products.[81,84,85] Although the overall estimate indicated no difference between high THC to CBD products versus placebo in likelihood of pain response (3 trials, N=143, RR 0.99, 95% CI 0.43 to 2.37; Appendix D, Figure D-10), the estimate was imprecise and statistical heterogeneity was present (I^2=72%). Two trials[84,85] found dronabinol for neuropathic pain associated with a nonstatistically significant decreased

likelihood of experiencing a pain response versus placebo (43% vs. 57%, RR 0.76, 95% CI 0.45 to 1.28 and 29% vs. 57%, RR 0.64, 95% CI 0.31 to 1.31). However, a small (n=26) low risk of bias RCT of patients with diabetic neuropathy found nabilone associated with a large increase in likelihood of pain response versus placebo (85% vs. 38%, RR 2.20, 95% CI 1.06 to 4.55).[81] In addition to inconsistency, pain response was only reported in three of seven RCTs, potentially introducing a form of selective reporting bias. Therefore, the strength of evidence for this outcome was insufficient.

Four RCTs reported on overall function (including pain interference) or disability.[81-83,85] A pooled analysis of three RCTs (N=98) found little difference between synthetic or purified high THC to CBD ratio products versus placebo for function, though the estimate was imprecise (0 to 10 scale, MD −0.18, 95% CI −1.25 to 0.77, I^2=51%; Appendix D, Figure D-11).[81,82,85] Two trials evaluated nabilone and one trial dronabinol. A fourth, small (n=13) RCT reported that neither high THC nor placebo was associated with change in disability, measured with the Barthel Index, but did not provide data.[83]

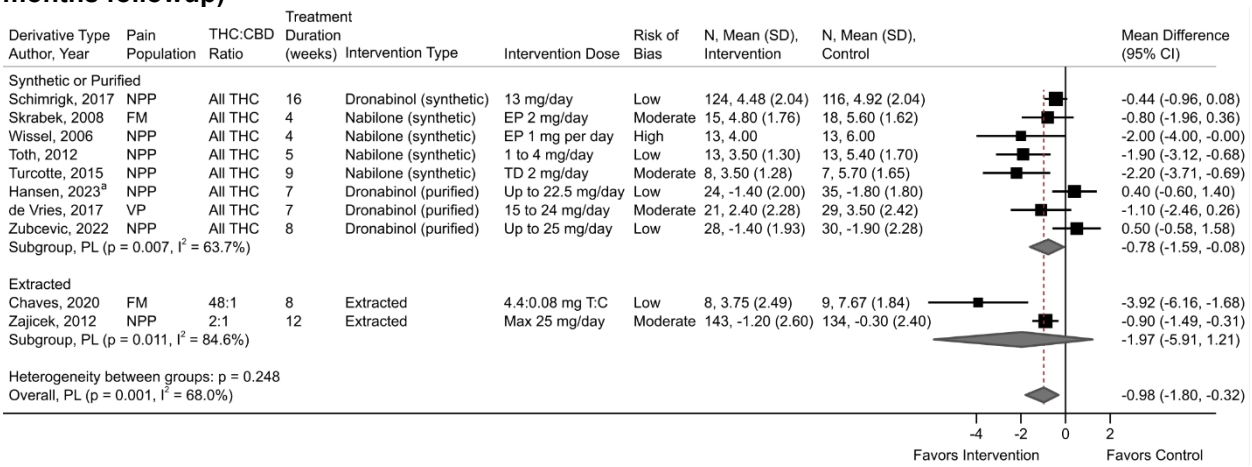
Few synthetic or purified THC studies reported secondary outcomes, with mixed results. A small (n=26), low risk of bias RCT of patients with diabetic neuropathy reported no difference between nabilone versus placebo in depression using the Hospital Anxiety and Depression-D [HADS-D] scale at 5 weeks (0 to 21 scale, MD −0.4, 95% CI −1.26 to 1.46), although there was a statistically significant improvement in anxiety (HADS-A, 0 to 21 scale, MD −2.9, 95% CI −3.80 to −2.0).[81] There was a statistically significant difference using the EQ-5D Index scores (0 to 1 scale [higher score indicating better quality of life], endpoint scores 0.74 vs. 0.60, p<0.05 using analysis of covariance [ANCOVA]). A small, moderate risk of bias study (n=40) of patients with fibromyalgia evaluated disease-specific function using the Fibromyalgia Impact Questionnaire (FIQ). The overall FIQ score (scale 0 to 100, higher score indicating greater impact of fibromyalgia on function) improved more at 4 weeks with nabilone than with placebo (MD −12.07, p<0.02). Nabilone was associated with a statistically significant improvement in FIQ anxiety scores after 4 weeks (0 to 10 scale, MD −2.2, p<0.01), but not in FIQ depression scores.[80] The three RCTs that permitted opioid use during the study period did not report effects on opioid use.[76,79,80] One low risk of bias RCT (n=58) found no differences between purified dronabinol versus placebo in sleep (0 to 10 scale, MD 0.36, 95% CI −1.31 to 2.03 on 0 to 10 scale), quality of life (0 to 10 scale, mean difference −0.35, 95% CI −1.66 to 0.97), Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety scores (MD 0.23, 95% CI −2.04 to 2.50), or PROMIS depression scores (MD 1.64, 95% CI −0.24 to 3.52).[85]

For adverse events, synthetic or purified THC was associated with a moderate increased risk of WAEs (6 RCTs, 14% vs. 7%, RR 1.92, 95% CI 1.10 to 4.80, I^2=0%, Appendix D, Figure D-12). Although the estimate for WAEs was statistically significant, some imprecision was present (the lower limit of the confidence interval crosses the threshold for a small effect) and the SOE was low. Of six RCTs reporting WAEs, two evaluated nabilone[80,82] (7% vs. 4%, RR 1.54, 95% CI 0.14 to 17.71, I^2=0%) and four evaluated synthetic or purified dronabinol[75,79,84,85] (15% vs. 7%, RR 1.95, 95% CI 1.08 to 6.55, I^2=0%, Appendix D, Figure D-13), with no statistically significant differences between nabilone or dronabinol (p=0.71). A pooled analysis of two RCTs (1 nabilone, 1 dronabinol) found synthetic THC associated with increased risk of any adverse event (2 RCTs, 86% vs. 71%, RR 1.20, 95% CI 0.96 to 1.48, I^2=0%, Appendix D, Figure D-14).[79,81] The estimate for SAEs was very imprecise (2 RCTs, N=312, 9% vs. 6%, RR 1.53, 95% CI 0.52 to 4.15).[79,84]

3.2.4 Results, Key Question 1 and Key Question 2. Benefits and harms of cannabinoids for treatment of chronic or subacute pain, summary of findings for high THC to CBD ratio

As in prior updates, synthetic or purified high THC to CBD ratio products were associated with statistically significant increased risk of dizziness (4 RCTs, 33% vs. 15%, RR 2.30, 95% CI 1.53 to 3.52, I^2=22%, Appendix D, Figure D-15)[75,79,84,85] and sedation (5 RCTs, 24% vs. 16%, RR 1.57, 95% CI 1.11 to 2.29, I^2=0%, Appendix D, Figure D-16).[75,79,80,84,85] The meta-analysis found synthetic or purified THC associated with large increased risk of nausea versus placebo (4 RCTs, 12% vs. 6%, RR 2.12, 95% CI 1.09 to 3.96, I^2=0%, Appendix D, Figure D-18).[75,79,84,85] Although the estimate for nausea was statistically significant, some imprecision was present and the SOE was low. A sensitivity analysis using the Bartlett's correction resulted in a more imprecise pooled estimate for sedation that was no longer statistically significant (sedation: 5 RCTs, RR 1.57, 95% CI 0.99 to 2.78, I^2=0%, Figure D-17; Table D-7). In stratified analyses for sedation, one study of nabilone (n=33) reported a greater magnitude of effect (RR 8.40, 95% CI, 1.16 to 60.84, Figure D-16) than four trials of dronabinol (N=425, RR 1.49, 95% CI 1.04 to 2.12, I^2=0%, Figure D-16), but there was no statistically significant subgroup difference (p=0.09).

Figure 4. Change in pain severity with high-THC ratio versus placebo (short term, 4 weeks to 6 months followup)


Derivative Type / Author, Year
Pain Population
THC:CBD Ratio
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean Difference (95% CI)
Synthetic or Purified
Schimrigk, 2017 NPP All THC 16 Dronabinol (synthetic) 13 mg/day Low 124, 4.48 (2.04) 116, 4.92 (2.04) -0.44 (-0.96, 0.08)
Skrabek, 2008 FM All THC 4 Nabilone (synthetic) EP 2 mg/day Moderate 15, 4.80 (1.76) 18, 5.60 (1.62) -0.80 (-1.96, 0.36)
Wissel, 2006 NPP All THC 4 Nabilone (synthetic) EP 1 mg per day High 13, 4.00 13, 6.00 -2.00 (-4.00, -0.00)
Toth, 2012 NPP All THC 5 Nabilone (synthetic) 1 to 4 mg/day Low 13, 3.50 (1.30) 13, 5.40 (1.70) -1.90 (-3.12, -0.68)
Turcotte, 2015 NPP All THC 9 Nabilone (synthetic) TD 2 mg/day Moderate 8, 3.50 (1.28) 7, 5.70 (1.65) -2.20 (-3.71, -0.69)
Hansen, 2023[a] NPP All THC 7 Dronabinol (purified) Up to 22.5 mg/day Low 24, -1.40 (2.00) 35, -1.80 (1.80) 0.40 (-0.60, 1.40)
de Vries, 2017 VP All THC 7 Dronabinol (purified) 15 to 24 mg/day Moderate 21, 2.40 (2.28) 29, 3.50 (2.42) -1.10 (-2.46, 0.26)
Zubcevic, 2022 NPP All THC 8 Dronabinol (purified) Up to 25 mg/day Low 28, -1.40 (1.93) 30, -1.90 (2.28) 0.50 (-0.58, 1.58)
Subgroup, PL (p = 0.007, I² = 63.7%) -0.78 (-1.59, -0.08)
Extracted
Chaves, 2020 FM 48:1 8 Extracted 4.4:0.08 mg T:C Low 8, 3.75 (2.49) 9, 7.67 (1.84) -3.92 (-6.16, -1.68)
Zajicek, 2012 NPP 2:1 12 Extracted Max 25 mg/day Moderate 143, -1.20 (2.60) 134, -0.30 (2.40) -0.90 (-1.49, -0.31)
Subgroup, PL (p = 0.011, I² = 84.6%) -1.97 (-5.91, 1.21)
Heterogeneity between groups: p = 0.248
Overall, PL (p = 0.001, I² = 68.0%) -0.98 (-1.80, -0.32)
-4
-2
0
2
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; T:C = THC to CBD; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain; WP = whole plant.

[a] Study is new to the 2024 update.

Active-control studies of synthetic THC versus noncannabinoids. Three previously included crossover RCTs compared synthetic THC versus other (noncannabinoid) medications. One low risk of bias RCT (n=80) found no statistically significant difference between nabilone (0.5 mg daily) versus ibuprofen (400 mg daily) in pain severity at 8 weeks in patients with medication overuse headache.[77] There were also no statistically significant differences in depression, anxiety, quality of life, risk of adverse events, or risk of WAEs; SAEs were not reported. At 2 weeks post study, nabilone was associated with lower daily analgesic intake than ibuprofen (0.89 vs. 1.34 analgesics daily; p=0.03). However, specific analgesic medications were not reported. Adverse events were infrequent and estimates were imprecise (dizziness 7.7% with nabilone vs. 0% with ibuprofen, cognitive deficits 3.8% vs. 0%, nausea 3.8% vs. 7.7%, and sedation 0% vs. 3.8%). A moderate risk of bias RCT (n=73) found dihydrocodeine (30 to 240 mg daily) associated with greater reduction in pain severity versus nabilone (max dose of 2 mg daily) at 6 weeks (VAS 0 to 100 scale; MD −5.7, 95% CI −10.9 to −0.5, p=0.03).[76] There were no statistically significant differences in secondary outcomes (depression, anxiety, quality of life, or

sleep). A very small (n=7), high risk of bias RCT found no difference between dronabinol versus diphenhydramine in pain intensity in patients with spinal cord injury.[78] Other efficacy outcomes were reported.

A moderate risk of bias, prospective observational study (n=101 for nabilone and gabapentin arms) found no difference between nabilone versus gabapentin in pain severity between groups at 3 months in patients with mixed neuropathic pain.[93] However, at 6 months nabilone was associated with a greater reduction in pain intensity (0 to 100 VAS, MD −5.8, 95% CI −10.18 to −1.42), and better sleep scores on the Medical Outcomes Study Sleep Scale (scale 0 to 60, MD −3.1, 95% CI −7.57 to 1.37) versus gabapentin, with no differences in pain interference, quality of life, depression, or anxiety. Nabilone was associated with decreased likelihood of any adverse event (38% vs. 48%, RR 0.72, 95% CI 0.49 to 1.07), WAEs (10% vs. 23%, RR 0.44, 95% CI 0.17 to 1.16), and sedation (35% vs. 60%, RR 0.58, 95% CI 0.37 to 0.91), although only the estimate for sedation was statistically significant. The likelihood of experiencing dizziness was similar for nabilone and gabapentin (33% vs. 39%, RR 0.85, 95% CI 0.50 to 1.44).

Head-to-head comparisons of cannabis-based products. Two low risk of bias RCTs compared purified oral dronabinol versus two low-THC products (synthetic oral CBD alone or purified THC plus synthetic CBD in a 1:2 ratio).[84,85] Median daily doses were 22.5 to 25 mg for THC, 45 to 50 mg for CBD, and 15 to 17.5 mg THC/30 to 35 mg CBD for the combination. Estimates for each product versus placebo for pain intensity, function, and secondary outcomes (sleep, quality of life, anxiety, and depression) were imprecise and had overlapping confidence intervals, indicating no statistically significant differences between products. There were no statistically significant differences between dronabinol and CBD or combined THC/CBD in likelihood of ≥30% improvement in pain score or adverse events in either trial, though estimates were imprecise.

A previously included retrospective cohort study (n=774) compared extracted nabiximols oromucosal spray (comparable THC to CBD ratio) with oral synthetic dronabinol (high THC to CBD ratio) in patients with neuropathic pain and inadequate pain relief with recommended first- and second-line treatments (e.g., nonopioid analgesics, opioid analgesics, antiseizure medications, or antidepressants), in a propensity matched analysis.[94] Mean age was 46 years, 57 percent of patients were female, and mean pain intensity at baseline was 4.4 (standard deviation 1.46) on a 0 to 10 scale. Mean daily doses were 16.6 mg THC/15.4 mg CBD for nabiximols, and 17.2 mg THC for dronabinol. At 24 weeks, nabiximols were associated with greater improvement in pain intensity than dronabinol, although the difference was below the threshold for a small effect (MD 3.5, 95% CI 1.6 to 5.4 on the Pain Intensity Index [0 to 100 scale]); there was a small improvement in function (76.0% vs. 68.3% on the modified Pain Disability Index, $p<0.001$). Nabiximols were also associated with greater improvements in quality of life, anxiety, and depression, and higher likelihood of discontinuing all rescue analgesics than dronabinol (75.6% vs. 45.9%, RR 1.7, $p<0.001$), as well as decreased likelihood of nervous system adverse events (9.5% vs. 19.9%, RR 0.48, 95% CI 0.32 to 0.71) and psychiatric adverse events (4.2% vs. 14.8%, RR 0.28, 95% CI 0.16 to 0.50). The study was rated moderate risk of bias; methodological limitations included failure to report attrition or missing data and unclear blinding of data analysts to interventions.

3.2.4.2 Extracted THC

Two previously included placebo-controlled RCTs (N=294) studied extracted high THC to CBD ratio products with different ratios of THC to CBD.[73,74] A 12-week, moderate risk of bias RCT of patients with pain due to MS (n=277) studied a product described as an extract from *Cannabis sativa L*. containing 2.5 mg of THC and CBD in the range of 0.8 to 1.8 mg per capsule (twice daily, titrated to a maximum of 25 mg daily) versus placebo.[74] More than half of enrolled patients were using an analgesic at baseline, but the type of analgesic or whether they could continue use during the trial was not reported. Patients using cannabis within 30 days of study enrollment were excluded. An 8-week, low risk of bias RCT of 17 patients with fibromyalgia studied low-dose, sublingual THC oil.[73] The product contained 24.44 mg/mL of THC and 0.51 mg/mL of CBD (THC to CBD ratio ~48:1), and small quantities of other cannabinoids. The mean daily dose in the active treatment group was 4.4 mg THC/0.08 mg CBD in the active treatment group. The dose of CBD in this preparation was described as being so low as to not contribute meaningfully to outcomes. Twenty-five percent of patients had used an opioid prior to the study, but opioid use during the trial was not reported.

In pooled analysis, pain severity was improved with the extracted high THC products, but the difference was not statistically significant (2 RCTs, 0 to 10 scale, MD −1.97, 95% CI −5.91 to 1.21, I^2=85%; Figure 4). There was a high degree of heterogeneity in this combined estimate, likely due to multiple differences between the studies, including sample size, dose, duration, and pain condition evaluated (fibromyalgia vs. MS), with a large difference in the magnitude of effect across the two studies. Individually, each study found a statistically significant reduction in pain severity. The 8-week, low-dose THC oil study of 17 women with fibromyalgia reported a larger effect (0 to 10 scale, MD −3.92, 95% CI −5.98 to −1.86)[73,74] on pain intensity than the larger (n=277) 12-week study of a much higher dose of a high-THC capsule product (MD −0.90, 95% CI −1.49 to −0.31).[73,74] Pain response was not reported.

In the RCT of patients with fibromyalgia, cannabis was not associated with improvement in physical functioning (1 RCT, FIQ physical functioning subscale [scale 0 to 10], MD 1.75, 95% CI −0.46 to 3.98) versus placebo, although the extracted product was associated with large improvement in overall quality of life (1 RCT, FIQ total [scale 0 to 100], MD 36.0, p=0.005).[73] However, there were some potentially important differences in baseline scores between groups. There were no differences between groups in measures of depression and anxiety, based on FIQ subscales.

In the RCT of patients with MS, the extracted high THC product was associated with higher risk of WAEs (13.9% vs. 5.7%, RR 3.12, 95% CI 1.54 to 6.33) and dizziness (62.2% vs. 7.5%, RR 8.34, 95% CI 4.53 to 15.34) versus placebo.[74] The estimate for SAEs was imprecise (4.9% vs. 2.2%, RR 2.19, 95% CI 0.58 to 8.28). In the RCT of patients with fibromyalgia, the extracted high THC product was associated with large increased risk of somnolence versus placebo (1 RCT, 88% vs 11%, RR 7.9, 95% CI 1.2 to 50.9).[73] Other adverse events of interest were not reported by either study.

3.2.4.3 Combined Analysis of Synthetic THC and Plant-Derived THC Products

To evaluate whether there was an effect for any form of high-THC product (synthetic, purified, or extracted), we combined results from all studies of high THC to CBD ratio interventions (Figure 4). The overall combined mean difference was −0.98 (95% CI −1.80 to −0.32, I^2= 68%), or similar to a prior pooled estimate (−1.12, 95% CI −1.97 to −0.48, I^2=65%). Although substantial statistical heterogeneity was present, a stratified analysis of synthetic or purified versus extracted forms of high THC (Appendix D, Table D-8) did not indicate a statistically significant subgroup difference (p=0.318). The number of RCTs included in the combined analysis (≥8 studies) allowed evaluation for publication bias using graphical and statistical methods. Both the funnel plot and the Egger test (p=0.131) suggested potential small sample effects, a marker for publication bias, though the p-value for the Egger test was above the threshold for statistical significance (Appendix I, Figure I-1).

3.2.5 Key Points for Low THC to CBD Ratio

- Synthetic or purified oral CBD alone was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale, MD 0.40, 95% CI −0.14 to 1.00, I^2=20%) (SOE: moderate), greater likelihood of pain response (4 RCTs, N=334, 37.0% vs. 44.4%, RR 0.84, 95% CI 0.62 to 1.10; I^2=0%) (SOE: moderate), or improved function (3 RCTs, N=272, standardized mean difference [SMD] 0.11, 95% CI −0.14 to 0.41, I^2=0%) (SOE: moderate) versus placebo. CBD was not associated with increased likelihood of any adverse event (2 RCTs, N=205, 71.3% vs. 59.6%, RR 1.12, 95% CI 0.93 to 1.49, I^2=0%) (SOE: moderate), dizziness (3 RCTs, N=206, 13.3% vs. 18.5%, RR 0.75, 95% CI 0.28 to 1.81, I^2=12%) (SOE: low), or sedation (3 RCTs, N=206, 16.3% vs. 19.4%, RR 1.07, 95% CI 0.21 to 1.93, I^2=34%) versus placebo (SOE: low).
- Combined oral purified THC (dronabinol) and synthetic CBD in ~1:2 ratio was not associated with decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%) (SOE: low), greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%) (SOE: low), or improved function (1 RCT, N=60, SMD 0.29, 95% CI −0.21 to 0.80, I^2=0%) (SOE: low) versus placebo, but estimates were imprecise. The low THC to CBD ratio combination was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I^2=0%) (SOE: moderate); combined low THC to CBD was also associated with a nonstatistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I^2=32%) (SOE: low) and sedation (2 RCTs, N=123, 43.1% vs. 29.2%, RR 1.55, 95% CI 0.86 to 2.72, I^2=0%) (SOE: low).
- One RCT (n=60) evaluated intraoral CBD for temporomandibular disorders, but had serious methodological limitations. In addition, the origin of the CBD (synthetic or plant-derived) was not reported, and it was unclear whether the CBD was intended to have systemic or only topical effects (SOE: insufficient).

3.2.6 Summary of Findings for Low THC to CBD Ratio

Seven previously included RCTs[85,86,88,89,84,87,90] evaluated short-term outcomes of low THC to CBD ratio products versus placebo. Four RCTs[84,85,87,88] evaluated oral products and two RCTs

evaluated nonoral products.[86,89] One RCT evaluated two intraoral products (unclear if effects intended to be systemic or only topical).[90] Regarding oral low-THC products, two RCTs (N=177),[84,85] including one RCT also included in the high-THC section,[84] evaluated synthetic oral CBD (median 45 or 50 mg daily) or the combination of purified oral THC (dronabinol, median 17.3 or 15 mg daily) plus synthetic CBD (median 35 or 30 mg daily) in a ~1:2 ratio in patients with neuropathic pain (due to MS or spinal cord injury in the new RCT, and peripheral neuropathic pain in the prior RCT). One RCT (n=158) evaluated synthetic oral CBD as add-on to usual analgesic regimen (not specified) in patients with hand osteoarthritis or psoriatic arthritis[88] and another RCT (n=86) evaluated purified oral CBD as add-on to acetaminophen in patients with knee osteoarthritis.[87] Another RCT (n=60) evaluated intraoral CBD (20 or 40 mg daily) for temporomandibular pain. The origin of the CBD products (synthetic or plant-derived) was not reported, and it was unclear if effects were intended to be systemic or only topical.[90] A small (n=15) RCT[86] evaluated extracted sublingual THC to CBD oil (1 to 6 ratio, median dose 15 mg THC to 90 mg CBD) or a more purified version of the same product (≥97% pure CBD and THC) in patients with chronic pain undergoing hemodialysis and another small (n=29) RCT evaluated topical CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo in patients with neuropathic pain.[89] Across trials, the median age ranged from 24 to 68 and the proportion of female patients ranged from 13 to 74 percent. Two trials excluded patients currently undergoing opioid treatment,[84,85] three trials allowed concomitant opioids or opioids as rescue medications,[86-88] and two trials did not report concomitant or rescue opioid use.[89,90] Three studies required patients to abstain from cannabis for at least 3 months to be eligible for enrollment,[84,86,90] three studies allowed previous use of cannabinoids,[85,88,89] and one study did not report prior cannabis use.[87] The availability in the United States of the low-THC products used in the RCTs is uncertain (no study evaluated a low-THC product approved by the FDA).

Among the RCTs that evaluated oral products, two were rated low risk of bias[84,85] and two were rated moderate risk of bias.[87,88] Two RCTs of nonoral products were rated high risk of bias, and one RCT of intraoral products was rated moderate risk of bias.[86,89,90] Methodological limitations in the high and moderate risk of bias RCTs included unclear randomization and allocation concealment methods, high or differential attrition, and unclear blinding of outcome assessors. In addition, a high risk of bias crossover RCT of sublingual CBD did not report outcomes for the initial (prior to crossover) period.[86] A high risk of bias RCT of topical CBD oil did not report all planned analysis, did not preregister its protocol, and raised important ethical concerns, as the study authors reported that they were unable to obtain institutional review board approval yet still carried out the trial.[89] Study details and results can be found in Appendix E, Tables E-1 to E-4, and risk of bias assessments are shown in Appendix F, Table F-1.

Placebo-controlled trials of synthetic or purified oral low-THC products. We analyzed trials of CBD alone separately from trials of combined THC plus CBD (ratio ~1:2). Oral synthetic or purified CBD was not associated with decreased pain intensity (4 RCTs, N=334, 0 to 10 scale MD 0.40, 95% CI −0.14 to 1.00, I^2=20%; Figure 5), greater likelihood of experiencing ≥30% improvement in pain (4 RCTs, N=334, 37.0% vs. 44.4%, RR 0.84, 95% CI 0.62 to 1.10; I^2=0%; Appendix D, Figure D-19),[84,85,87,88] or improved function (3 RCTs, N=272, SMD 0.11, 95% CI −0.15 to 0.41, I^2=0%; Appendix D, Figure D-20) versus placebo, with point estimates favoring placebo.[85,87,88] CBD was also not associated with increased likelihood of any adverse event (2 RCTs, N=205, 71.3% vs. 59.6%, RR 1.12, 95% CI 0.93 to 1.49, I^2=0%; Appendix D, Figure D-21),[87,88] dizziness (3 RCTs, N=206, 13.3% vs. 18.5%, RR 0.75, 95% CI 0.28 to 1.81, I^2=12%;

Appendix D, Figure D-22),[84,85,87] or sedation (3 RCTs, N=206, 16.3% vs. 19.4%, RR 1.07, 95% CI 0.21 to 1.93, I^2=34%; Appendix D, Figure D-23),[84,85,87] though estimates were imprecise. Estimates for SAEs (Appendix D, Figure D-24),[84,85,87] WAEs (Appendix D, Figure D-25),[84,85,87,88] and nausea (Appendix D, Figure D-26)[84,85,87] were too imprecise to inform reliable conclusions. Three of the RCTs evaluated synthetic CBD and one RCT[87] evaluated purified synthetic equivalent CBD. Restricting the analysis to trials of synthetic CBD resulted in similar findings (for pain intensity, 3 RCTs, N=248, MD 0.51, 95% CI −0.23 to 1.34, I^2=36%; Appendix D, Figure D-27).

The combination of plant-derived, synthetic equivalent THC (dronabinol) and synthetic CBD (~1:2 ratio) was also not associated decreased pain intensity (2 RCTs, N=113, 0 to 10 scale, MD 0.12, 95% CI −0.71 to 0.93, I^2=0%; Figure 5),[84,85] greater likelihood of experiencing ≥30% improvement in pain (2 RCTs, N=123, 55.2% vs. 50.8%, RR 1.07, 95% CI 0.73 to 1.57, I^2=0%; Appendix D, Figure D-28),[84,85] or improved function (1 RCT, n=60, SMD 0.29, 95% CI −0.21 to 0.80, I^2=0%; Appendix D, Figure D-29)[85] versus placebo. However, each estimate was based on only one or two RCTs and was imprecise. Estimates for SAEs (Appendix D, Figure D-24) and WAEs (Appendix D, Figure D-30) were extremely imprecise. The combined low THC to CBD ratio intervention was associated with increased risk of nausea versus placebo (2 RCTs, N=123, 24.1% vs. 6.2%, RR 3.80, 95% CI 1.08 to 17.05, I^2=0%; Appendix D, Figure D-26);[84,85] low THC to CBD was also associated with a nonstatistically significant increase in risk of dizziness (2 RCTs, N=122, 35.1% vs. 23.1%, RR 1.74, 95% CI 0.47 to 3.46, I^2=32%; Appendix D, Figure D-31) and sedation (2 RCTs, N=123, 43.1% vs. 29.2%, RR 1.55, 95% CI 0.86 to 2.72, I^2=0%; Appendix D, Figure D-32).[84,85]

Evidence on secondary outcomes was limited. One RCT (n=86) found no difference between purified CBD versus placebo in SF-36 Physical (0 to 100 scale, MD 0.65, 95% CI −3.6 to 4.9) or Mental (0 to 100 scale, MD 1.85, 95% CI −1.2 to 4.9) Component Summary scores.[87] One RCT (n=87) found no difference between either synthetic CBD alone or the combination of purified THC plus CBD versus placebo in mood or quality of life.[85] CBD alone, but not the combination, was associated with statistically significant improvement in sleep versus placebo (0 to 10 scale; CBD: MD 2.03, 95% CI 0.35 to 3.71; THC/CBD: MD 0.89, 95% CI −0.64 to 2.42). Another RCT (n=129) found no differences between synthetic CBD versus placebo in sleep quality, depression or anxiety.[88]

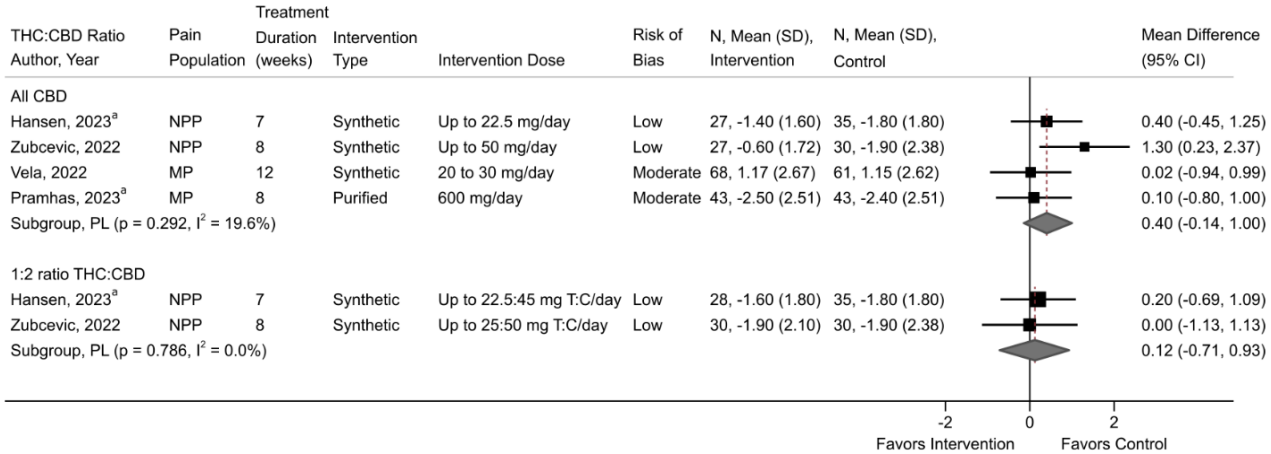
Placebo-controlled trials of extracted low-THC products. A small (n=15) high risk of bias crossover RCT (n=15) evaluated two low THC to CBD ratio products versus placebo.[86] The products were extracted sublingual THC to CBD oil [1:6 ratio] or the same product with further purification (≥97% pure CBD and THC). Maximum daily doses were 18 drops per day (15 mg THC/90 mg CBD). The study used a crossover design consisting of two 16-week treatment periods with a 2-week washout. Estimates for pain severity at the end of treatment were imprecise and indicated no statistically significant between-group differences; pain response and function were not reported. There were too few cases of SAEs or WAEs to evaluate these outcomes and specific harms were not reported.

A small (n=29), high risk of bias RCT evaluated extracted topical CBD cream in patients with neuropathic pain (mean age 68 years, 38% female).[89] Patients were randomized to 4 weeks of CBD cream (250 mg/3 oz) applied to symptomatic areas up to 4 times daily or placebo (total

daily dose received not reported). CBD was associated with significantly greater improvement in pain intensity versus placebo (−1.34 vs. −0.59, p=0.009 by ANCOVA). However, this trial was difficult to interpret because it was unclear if the topical CBD oil was intended to have local or systemic effects, and details regarding the extraction process and extent of purification were not reported. It was also unclear if the analysis included a crossover extension phase in which patients initially randomized to placebo were given CBD. The RCT did not report pain response, pain interference, overall function/disability, or secondary outcomes, and no adverse events were reported.

Placebo-controlled trials of low-THC products of unknown origin. One moderate risk of bias RCT (n=60) evaluated two low THC to CBD ratio products versus placebo in patients with temporomandibular pain (mean age 24 years, 60% female).[90] The products were an intraoral gel with CBD concentrations of 5 or 10 percent.[90] It was unclear whether the CBD gel was intended to have local or systemic effects, and details regarding the source of the CBD (synthetic or plant-derived) were not reported. Patients receiving the 10 percent CBD gel used 20 mg per masseter muscle intraorally, for a total of 40 mg of CBD per day. Patients receiving the 5 percent CBD gel used a total of 20 mg of CBD per day. CBD was associated with significantly greater improvement in pain severity versus placebo after 30 days (median 6.0 vs. 2.0 for 10% CBD, 6.0 vs. 3.5 for 5% CBD, 6.0 vs. 5.5 for placebo).[90]

Figure 5. Change in pain severity with oral low-THC ratio products versus placebo (short term, 4 weeks to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean Difference (95% CI)
All CBD
Hansen, 2023[a] NPP 7 Synthetic Up to 22.5 mg/day Low 27, -1.40 (1.60) 35, -1.80 (1.80) 0.40 (-0.45, 1.25)
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Low 27, -0.60 (1.72) 30, -1.90 (2.38) 1.30 (0.23, 2.37)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day Moderate 68, 1.17 (2.67) 61, 1.15 (2.62) 0.02 (-0.94, 0.99)
Pramhas, 2023[a] MP 8 Purified 600 mg/day Moderate 43, -2.50 (2.51) 43, -2.40 (2.51) 0.10 (-0.80, 1.00)
Subgroup, PL (p = 0.292, I² = 19.6%) 0.40 (-0.14, 1.00)
1:2 ratio THC:CBD
Hansen, 2023[a] NPP 7 Synthetic Up to 22.5:45 mg T:C/day Low 28, -1.60 (1.80) 35, -1.80 (1.80) 0.20 (-0.69, 1.09)
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Low 30, -1.90 (2.10) 30, -1.90 (2.38) 0.00 (-1.13, 1.13)
Subgroup, PL (p = 0.786, I² = 0.0%) 0.12 (-0.71, 0.93)
-2
0
2
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; T:C = THC to CBD; THC = tetrahydrocannabinol.
[a] Study is new to the 2024 update.

3.2.7 Key Points for Other or Mixed Cannabinoids

- Six cohort studies (N=34,374), including three new studies, of various or mixed cannabinoids, had methodological limitations and provided insufficient evidence to draw conclusions regarding effects on pain, function, and adverse events (including cardiovascular events).
- Three short-term RCTs of CBDV (n=31), hemp seed oil (new; n=90), or THC:CBD:CBN (new; n=93) provided insufficient evidence to draw conclusions.

3.2.8 Summary of Findings for Other or Mixed Cannabinoids

Three new cohort studies evaluated patients using various cannabis products (Appendix E, Table E-5), but had serious methodological limitations and were not primarily designed to report how outcomes differed according to the product used.[4-6] One new high risk of bias cohort study (n=96) evaluated the association between prescribed medical cannabis use and changes in pain and mental health in Australian patients with chronic pain.[6] Mean age was 52 and women comprised 53 percent of the study population. Patients were categorized according to the THC:CBD ratio (high, comparable, or low); patients who took medications from different categories comprised a "mixed" group. Pain and function outcomes were not reported by cannabis category; therefore, results were only available for adverse events. The most common adverse events were dry mouth (18% in THC dominant group, 17% in CBD dominant group, 12% in the balanced group, and 23% in the mixed group), sleepiness (14% vs. 16% vs. 12% vs. 14%), increased appetite (11% vs. 8% vs. 12% vs. 14%), and "feeling high" (16% vs. 4% vs. 6% vs. 7%). Another new high risk of bias cohort study (n=148) evaluated different extracted products in patients with fibromyalgia.[5] Median age was 47 years and women comprised 80 percent of the study population. There was no difference between plant-derived oil, dried flower, or both in Fibromyalgia Symptom Score at 1, 3, 6, or 12 months (at 12 months, mean change from baseline on 0 to 31 scale −1.2, −1.9, and −2.2, respectively; p=0.36 for between-group difference). Other results were not reported by cannabis product. A third new moderate risk of bias cohort study (n=741) evaluated medical cannabis use in patients with mixed chronic pain conditions.[4] Mean age was 39 years and women comprised 63 percent of the study population. Patients were categorized according to the THC:CBD ratio (high, comparable, or low), but the study used a different categorization scheme than the one used in this review. High THC:CBD was considered a 5:1 or greater ratio of THC to CBD; balanced THC:CBD was considered less than 5:1 and greater than 1:5 ratio of THC to CBD; and high CBD was considered a 1:5 or lower ratio of THC to CBD. In a linear mixed model of outcomes through 40 months, differences between balanced or high THC products versus high CBD products on pain were trivial (less than 0.10 point reduction on a 0 to 10 scale). Other outcomes, including harms, were not reported. Methodological limitations in the cohort studies included unclear methods for ascertaining potential confounders, unclear reporting of attrition or missing data, and unclear blinding practices (Appendix F, Table F-2).

Three other cohort studies were included in prior updates. A large (n=32,332) cohort study evaluated the association between medical cannabis use and arrhythmia or ischemic coronary disease in Danish patients with chronic pain (Appendix E, Table E-5).[95] Median age was 59 years and women comprised 63 percent of the study population. The pain conditions varied (39% musculoskeletal, cancer 17%, neurological 13%, and unspecified 31%). Patients who newly used medical cannabis were matched to controls not using patients on age, sex, chronic pain diagnosis, and use of other pain medications. Use of any medical cannabis was associated with increased 180-day risk of new-onset arrythmia versus no medical cannabis (0.8% vs. 0.4%, adjusted RR 2.07, 95% CI 1.34 to 2.80), after adjusting for comorbidities, educational level, and age; there was a small, non-statistically significant increase in180-day risk of acute coronary syndrome (adjusted RR 1.20, 95% CI 0.35 to 2.04). Rates of new-onset arrhythmia were similar when patients were stratified according to cannabinoid type (CBD alone, THC alone, or mixed THC/CBD). The study was rated moderate risk of bias; methodological limitations included

unclear blinding of outcomes assessors or data analysis and failure to report attrition or missing data (Appendix F, Table F-2).

A cohort study (n=296 for primary analysis) compared outcomes of various oral and inhaled cannabis products (ranging from low to high THC to CBD ratio) in an Australian cohort of patients with various types of chronic pain.[96] Although outcomes for pain intensity, pain interference, and physical function were somewhat better in the comparable THC to CBD and low THC to CBD ratio groups compared to the high THC to CBD ratio group, the study was rated high risk of bias due to serious methodological limitations, including failure to control for confounders (Appendix F, Table F-2).

A moderate risk of bias prospective cohort study (n=761) evaluated different cannabis products for patients with chronic pain (mixed conditions) in the UK Medical Cannabis Registry.[97] It compared an inhaled dry flower, sublingual cannabis oils, or both. The oils varied in composition, with some only containing THC or CBD, and some with THC to CBD ratios that ranged from 1:1 to 1:20. The mean age was 47, and 47 percent of participants were female. Race was not reported. In multivariate analysis, there were no differences between arms in likelihood of experiencing improvement in Brief Pain Inventory [BPI] pain severity (adjusted odds ratio [OR] 1.36, 95% CI 0.51 to 3.65 for combination versus oils and 2.12, 95% CI 0.28 to 16.11 for dried flower versus oils) or interference (adjusted OR 1.90, 95% CI 0.68 to 5.29 for combination versus oils and 1.61, 95% CI 0.21 to 12.18 for dried flower versus oils), though estimates were imprecise and favored the combination and dried flower over oils alone. There was no difference between the combination versus oils alone in likelihood of experiencing an adverse event, though this estimate was also imprecise (adjusted OR 1.00, 95% CI 0.64 to 1.58).

One new, moderate risk of bias RCT (n=90) evaluated plant-derived topical hemp seed oil, diclofenac 1% gel or placebo (each dosed at 10 drops daily) for 8 weeks in patients with knee osteoarthritis (Appendix E, Table E1-E4, Appendix F, Table F-1).[1] Mean age was 57 years and 77 percent of participants were female. Both hemp seed oil and diclofenac gel were associated with lower pain scores versus placebo at 8 weeks (mean 3.53 vs. 3.37 vs. 5.30 on 0 to 10 scale, respectively; p=0.001 for between-group difference), although outcomes were very similar for hemp seed oil and diclofenac gel. Similar findings were reported for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical activity (scale 0 to 68, mean 22.39 vs. 21.23 vs. 29.43, respectively; p=0.001 for between-group difference) and total WOMAC (scale 0 to 96, mean 30 vs. 28.20 vs. 42.27, p=0.001 for between-group difference). No adverse events were reported in any group.[1]

Another new, moderate risk of bias RCT (n=93) compared purified, topical THC:CBD:CBN oil (3.20:0.32:0.65 ratio) versus placebo for 12 weeks in patients with diabetic neuropathy (Appendix E, Table E1-E4, Appendix F, Table F-1).[2] The dose ranged from 1 to 2 drops for patients with mild pain to 5 to 6 drops for patients with severe pain. Mean age was 64 years and 73 percent were female. THC:CBD:CBN was associated with improved Neuropathic Pain Symptom Inventory-Thai Version scale score (mean difference -17.28, 95% CI -21.49 to -13.07). The likelihood of any adverse event was similar (10% vs. 10%, RR 1.0, 95% CI 0.31 to 3.24). Specific adverse events were not reported.

A previously included small (n=31), moderate risk of bias trial evaluated oral CBDV (described as "a novel phytocannabinoid derived from the *Cannabis sativa* L. plant").[91] Patients

with HIV-related chronic pain (mean age 50 years, 3% female) were randomized to oral CBDV oil (50 mg/ml) dosed at 8 ml daily (400 mg CBDV) or placebo oil for 4 weeks, then crossed over after a 21-day washout. Using the numerical rating scale (NRS) pain scale (10-point scale), statistically significantly fewer patients achieved response (≥30% pain reduction) with CBDV compared with placebo (38% vs. 81%, RR 0.46, 95% CI 0.24 to 0.91). There was no difference between CBDV and placebo in change in pain severity from baseline (MD 0.62, 95% CI −0.05 to 1.32). Secondary outcomes of anxiety, depression, and insomnia also were not statistically different between groups. Although more patients randomized to CBDV reported any adverse event than placebo (91% vs. 79%), the difference was not statistically significant (p=0.28). Other adverse events occurred slightly more often in the CBDV groups than placebo, but few events were reported (WAEs, 1 vs. 0; SAEs, 1 vs. 0; diarrhea, 3 vs. 0; dry mouth, 3 vs. 0).

3.2.9 Key Point for Whole-Plant and Unspecified (Patient-Choice) Cannabis Products

- There was insufficient evidence to draw conclusions about the effectiveness and harms of whole-plant cannabis products or patient-choice cannabis products in treating chronic pain.

3.2.10 Summary of Findings for Whole-Plant and Unspecified (Patient-Choice) Cannabis Products

No new study evaluated whole-plant or unspecified (patient-choice) cannabis products. Six previously included observational studies (N=12,939) reported on the effects of cannabis, with five (3 high, 2 moderate risk of bias) studies evaluating medical cannabis programs (cannabis product unspecified)[98-100] or self-reported use of cannabis (product unspecified),[101,102] and one moderate risk of bias study evaluating a specific whole-plant cannabis product.[103] Patient characteristics are summarized across studies in Table 5. The type of pain was not well reported. Mean age was 53 years, and 55 percent were female. Baseline pain was 5.35 (95% CI 4.56 to 8.00) on a 0 to 10 scale. One study evaluated outcomes at 3 months (short duration),[100] and the other five were longer duration (1 to 4 years followup).[98,99,101-103] The three studies of medical cannabis programs allowed patients to self-select the cannabis products they used and compared them with patients who chose not to enroll in the programs (assumed to be no cannabis use).[98,99,103] Two of the studies were retrospective analyses of larger prospective cohort studies of patients with chronic pain taking opioids,[101,102] based on patient self-report of cannabis use, but specific products used were not reported. In the study of a whole-plant cannabis product, the cannabis group received herbal cannabis containing 12.5 percent (+/- 1.5%) THC.[103] Total daily doses received were reported in two studies with one reporting 93 mg of THC per week (mean) in a medical cannabis program,[100] and the other reporting 2.5 grams per day of a whole-pant cannabis product (dose confirmed with study authors).[103]

Two studies reported on primary pain or function outcomes. A high risk of bias before-after study (n=46) found medical cannabis use (product type and dose not specified), but not usual care without cannabis, associated with improvement from baseline in pain severity, pain-related disability, quality of life, depression, anxiety, and sleep.[100] However, only nine patients received

usual care and the study did not attempt to statistically compare results of medical cannabis versus usual care or account for potential confounders. A moderate risk of bias study of individuals using opioids also reported no statistically significant differences on pain or pain interference outcomes between frequent cannabis users (daily or near-daily)[101] and nonusers over 4 years of followup. Because the number of patients enrolled changed from year to year along with their cannabis use status, these analyses were conducted based on use in the prior 12 months.

A high risk of bias cohort study (n=431) of a whole-plant cannabis product with 12.5 percent THC (amount of CBD not reported) with 52 weeks of followup reported adverse events.[103] Patients in whom standard treatments were not effective were enrolled, with patients already using cannabis for pain preferentially enrolled in the treatment group. The median dose was 2.5 g of herbal cannabis per day (confirmed with study authors as amount dispensed). There was no difference between whole-plant cannabis use versus non-use in rates of any adverse event, SAEs, or dizziness. Both nausea (16.7% vs. 9.7%, RR 1.72, 95% CI 1.04 to 2.85) and sedation (13.5% vs. 4.6%, RR 2.91, 95% CI 1.46 to 5.83) were reported significantly more frequently in the cannabis group. Study WAEs were poorly reported for the usual care group and occurred in 4.7 percent of those using cannabis.

Four observational studies reported on the association between cannabis use (product unspecified) and opioid use for chronic pain.[98,99,101,102] The studies used different methods and reported outcomes differently, with no consistent direction of effect across the studies. A large, moderate risk of bias, retrospective cohort study (n=10,746) with propensity matching found a nonstatistically significant decrease in weekly oral morphine equivalent (OME) doses with cannabis use versus non-use (−183.2 OME, 95% CI −449.8 to 83.3). Preplanned subgroup analyses found that patients taking lower initial doses of opioids (<50 OME weekly) increased opioid use after medical cannabis authorization, while those using higher doses at baseline (>100 OME weekly) had a decrease (−435.5, 95% CI −596.8 to −274.2). Discontinuation of prescription opioids was less likely in the cannabis group versus the control group (49.3% vs. 72.3%, adjusted OR 0.38, 95% CI 0.34 to 0.41).

In a moderate risk of bias study (n=1,514 at baseline, 1,217 at year 4) of individuals with chronic pain using opioids, a statistically nonsignificant difference in OME use at 1 year was found between patients reporting daily or near daily cannabis use (type and dose not reported) and those reporting no use.[101] The adjusted mean daily OMEs were 97.1 in frequent cannabis users and 85.5 in nonusers (difference 32.76 mg daily, 95% CI, −25.04 to 90.57).

A high risk of bias, 52-week, prospective cohort study of patients with HIV-related chronic pain (n=433) evaluated the effect of cannabis use.[102] At baseline 47 percent were using an opioid for chronic pain. Among daily or near daily cannabis users also using opioids, the adjusted OR for discontinuing opioids was 1.67 (95% CI 0.52 to 5.37). Among daily or near daily cannabis users not using opioids at baseline, the adjusted OR for initiating an opioid was 2.29 (95% CI 0.86 to 6.16). Impact on morphine equivalents were not reported.

In a small (n=66), high risk of bias, retrospective cohort of patients in a medical cannabis program for low back pain, compared with patients who declined to participate, those in the cannabis program were more likely to reduce their daily opioid dose than the control group (83.8% vs. 44.8%, OR 5.12, 95% CI 1.56 to 16.88).[99] The reduction in dose was small, but statistically significant (MD −0.64 mg intravenous morphine equivalent, 95% CI −1.10 to −0.18 from starting mean doses in the two groups of 24.4 mg vs. 16.2 mg).

3.3 Key Question 3 and Key Question 4. In adults or adolescents with chronic or subacute pain, what are the benefits (Key Question 3) and harms (Key Question 4) of kratom or other plant-based substances for treatment of chronic or subacute pain?

3.3.1 Key Point

- No studies of kratom or other plant-based substances with properties similar to cannabis were found.

3.3.2 Summary of Findings

No evidence was found for kratom or other plant-based substances.

4. Discussion

4.1 Findings in Relation to the Decisional Dilemmas

The key decisional dilemmas for treating chronic and subacute pain with plant-based compounds include their effectiveness and safety and the effect of route of administration, formulation, dose or potency of products, types of pain, and other patient characteristics on outcomes, including harms. Important harms include typical adverse effects such as dizziness, sedation and nausea, but may also include more serious risks, such as cannabis use disorder (CUD), psychosis, and cognitive impairment. Potential benefits and harms must be considered in the context of frequent, possibly daily, long-term use. This update did not identify studies of plant-based compounds other than cannabis. Six new studies were added for this update: one placebo-controlled randomized controlled trial (RCT) of purified topical tetrahydrocannabinol (THC) to cannabidiol (CBD) to cannabinol (CBN) (THC:CBD:CBN);[2] one placebo-controlled RCT of plant-derived hemp seed oil;[1] one head-to-head RCT of a purified inhaled comparable THC:CBD ratio (6.3% THC, 8% CBD) product versus oxycodone or both;[3] one observational study of plant-extracted cannabis oil, dried flower, or both;[5] and two observational studies comparing various cannabis products (high, comparable, or low THC:CBD ratio, or mixed).[6] The new studies did not change the main findings of this review. Although the new placebo-controlled RCTs evaluated cannabis product categories new to this review, the strength of evidence (SOE) for each was insufficient because findings were based on a single trial with small sample sizes and methodological shortcomings.[1,2] The head-to-head trial found no difference in pain between a comparable ratio product, oxycodone, or both, but also had methodological limitations.[3] The observational studies had serious methodological shortcomings and were very limited in their reporting of comparative outcomes between different cannabis products.[5,6]

The main findings of this review are based on previously included evidence. Our findings are most applicable to short-term treatment (1 to <6 months), in adults with chronic pain (mainly neuropathic pain) compared with placebo. Although the scope of this living review was expanded in 2023 to include subacute pain and adolescents, no studies addressing these populations have been identified. Change in pain severity was reported across all studies, but other pain-related and overall functional outcomes (including pain interference) were reported sporadically.

Based on previously reviewed evidence, extracted comparable THC to CBD ratio oromucosal spray is probably associated with small improvements in pain severity (SOE: moderate) versus placebo in the short term. Although results for overall functioning also favored the comparable ratio oromucosal spray, the effect was slightly below the threshold for a small effect (SOE: moderate). Extracted comparable THC/CBD ratio oromucosal spray may also be associated with a moderate to large increased risk of dizziness (SOE: low), sedation (SOE: low), and nausea (SOE: low) versus placebo, with no effect on serious adverse events (SAEs) or study withdrawal due to adverse events (WAEs). There was a small increase in the proportion of patients with at least 30 percent improvement in pain (pain response) versus placebo; however, the finding was not statistically significant due to imprecision, and the SOE was low.

Synthetic or purified oral THC (high THC to CBD ratios) products may be associated with a small improvement in pain severity and no effect on overall function (SOE: low). Stratified analyses of placebo-controlled synthetic and purified THC trials indicated that synthetic THC (primarily nabilone) was associated with reduced pain intensity, while there was no clear effect

on pain intensity for purified dronabinol. This finding was from placebo-controlled trials and not based on head-to-head comparisons and should be interpreted with caution. There were inconsistent findings from three RCTs of high THC to CBD ratio products and likelihood of pain response, resulting in insufficient evidence to determine effects. As in prior updates, synthetic or purified oral THC products are probably associated with a large increase in risk of dizziness (SOE: moderate) and moderate increased risk of sedation (SOE: low). Although findings from updated meta-analyses became statistically significant for increased risk of WAEs and nausea in 2024, the magnitude of effect was unchanged from prior updates (moderate for WAEs and large for nausea) and imprecision remained present because the lower limit of the confidence interval (CI) for these outcomes crossed the threshold for a small effect. Therefore, the SOE for these outcomes remained low. For secondary outcomes, evidence with the addition of the new RCT remained very limited with no clear effect on quality of life, sleep, depression, or anxiety.

Based on previously reviewed evidence, extracted high THC to CBD ratio products may be associated with large increases versus placebo in risk of study WAEs and dizziness (SOE: low). There was insufficient evidence to determine effects on pain. Combining the evidence for all high THC to CBD ratio products resulted in a small improvement in pain severity, with a low SOE.

Meta-analyses for low THC to CBD ratio products found that neither oral synthetic or purified CBD alone nor oral purified THC (dronabinol) in combination with CBD (ratio ~1:2) was associated with decreased pain intensity, greater likelihood of pain response, or improved function versus placebo (SOE: moderate for oral CBD alone, low for combined THC/CBD). THC/CBD, but not CBD, was associated with increased risk of nausea (SOE: moderate), dizziness (SOE: low), and sedation (SOE: low). Although one RCT evaluated topical (intraoral) CBD for temporomandibular disorders, the sample size was relatively small, the trial had serious methodological limitations, the origin of CBD (synthetic or plant-derived) was not reported, and it was unclear if effects were intended to be systemic or only topical.[90]

Evidence on whole-plant cannabis, unspecified cannabis products (e.g., patient-choice), extracted and topical low THC to CBD ratio products, other cannabinoids (cannabidivarin [CBDV]), and comparisons with other active interventions or between cannabis-based products remained insufficient to draw conclusions. Evidence for other outcomes reported for comparable THC to CBD and high THC to CBD ratio products was also insufficient (see Appendix G for details).

Other adverse events (psychosis, CUD, cognitive deficits) and secondary outcomes were not reported for specific products. One cohort study found medical cannabis use (various THC to CBD ratio categories) associated with increased 180-day risk of arrhythmia versus nonuse, but not acute coronary disease.[95]

The 2022 updated Centers for Disease Control and Prevention guideline on opioids for pain does not make recommendations on cannabis for pain. Other guidance has been inconsistent. The 2019 U.K. National Institute for Health Care and Excellence clinical practice guideline[104] included a strong recommendations against use of cannabis for pain outside of clinical trials, though the guideline has been challenged as overly restrictive.[105] In 2021, an international guideline funded by a cannabis research center issued a weak recommendation for use of noninhaled medical cannabis for chronic pain when standard care is not sufficient.[106] Most recently, in 2025 the American College of Physicians advised, based in part on this living review, that clinicians counsel patients about the benefits and harms of cannabis or cannabinoids for chronic pain, including subgroups in whom harms are unlikely to outweigh benefits (young

adult and adolescent patients, patients with current or past substance use disorder, patients with serious mental illness, and frail patients or those at risk of falling); advised against cannabis or cannabinoids for chronic pain in patients pregnant, breastfeeding, or likely to conceive; and advised against use of inhaled cannabis.[107] Additionally, there have been multiple systematic reviews conducted on the use of cannabinoids to treat chronic pain, including a 2015 publication in the Journal of the American Medical Association, a 2018 Cochrane review, and a 2017 Veterans Affairs Evidence Synthesis Program review.[8,108-110] These high-quality reviews found generally similar results as this living review indicating some benefit in pain outcomes, primarily for short-term treatment in patients with neuropathic pain. However, the prior reviews combined all forms of cannabinoids in meta-analyses. Our review has more stratified results based on prespecified THC to CBD ratio categories, leading to higher strength of evidence ratings in some cases.[8] In addition, some higher-quality reviews are not current and are missing newer evidence. Multiple additional systematic reviews examining the of cannabis for chronic pain were published in or after 2020; overall, the findings of these reviews are also generally consistent with our findings.[111-117] One of the reviews which conducted meta-regression found that the impact on pain was similar between neuropathic and nonneuropathic pain populations[113] and that pain reduction was of a small magnitude and similar across formulations (inhaled, oral, oromucosal spray).

Our review did not identify eligible evidence on kratom to treat chronic pain. Two recent reviews of kratom provided limited information, and are based on noncomparative data or pharmacological data.[37,38] One evaluated surveys, cross-sectional studies, and poison-control center studies on the use of kratom; the other is a nonsystematic review addressing pharmacology, pharmacokinetics, prevalence and type of usage, and harms evidence.[37,38] Both found that patients report using kratom as a substitute for opioids apparently as a treatment for self-diagnosed opioid addiction or dependence in Thailand and Malaysia. They reported growing use in the United States for chronic pain and for recreational purposes. They also suggested that kratom may have addictive properties itself with symptoms of physiological withdrawal being common. Nonserious adverse effects include hyperpigmentation of the skin, constipation, weight loss, insomnia, xerostomia, and loss of libido. Poison control center data indicated a recent increase in calls involving kratom with multi-substance exposures involving kratom associated with a statistically significant increase in a serious medical event. In cases where kratom was the only substance involved (N=1,174), symptoms included agitation or irritability (23%), tachycardia (21%), nausea (15%), drowsiness/lethargy (14%), vomiting (13.2%), confusion (11%), hypertension (10%), and seizures (10%).[38]

Tables 6 and 7 provide a summary of the evidence for primary outcomes and harms related to cannabis interventions. Additional details on the SOE for these outcomes are located in Appendix G.

Table 6. Key Question 1: Benefits of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
Comparable THC/CBD - Extracted, Oromucosal Spray	Potential effect (4)[b] [✓]	Small effect (7) [✓✓]	No effect[c] (6) [✓✓]
High THC – Synthetic or Purified, Oral	Insufficient (3, 1 new)	Small effect (8, 1 new) [✓]	No effect (4) [✓]

4. Discussion

Product, THC to CBD Ratio	Pain Response[a] Effect Size (N Studies) [SOE]	Pain Severity Effect Size (N Studies) [SOE]	Function Effect Size (N Studies) [SOE]
High THC – Extracted, Oral	No evidence	Insufficient (2)	Insufficient (1)
Low THC – Extracted CBD, Topical	No evidence	Insufficient (1)	No evidence
Low THC – Synthetic or Purified, Oral[d]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (4, 2 new)[e]** [✓✓]	**No effect (3, 1 new)[e]** [✓✓]
Low THC – Synthetic CBD Plus Purified THC, Oral[f]	**No effect (2, 1 new)[e]** [✓]	**No effect (2, 1 new)[e]** [✓]	**No effect (1)[e]** [✓]
Low THC – Sublingual CBD/THC, Extracted	No evidence	Insufficient (1)	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	**Insufficient (1 new)[e]**	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence
Whole-Plant Cannabis (12% THC)[g]	No evidence	Insufficient (1)	No evidence
Other cannabinoids – Hemp Seed Oil, Topical	No evidence	**Insufficient (1 new)[e]**	**Insufficient (1 new)[e]**
Other Cannabinoids – THC:CBD:CBN, Topical	No evidence	**Insufficient (1 new)[e]**	No evidence

Abbreviations: CBD = cannabidiol; CBN = cannabinol; CBDV = cannabidivarin; SOE = strength of evidence; THC = tetrahydrocannabinol.
[a] ≥30% improvement from baseline
[b] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[c] The pooled difference of -0.42 (95% CI -0.73 to -0.16) was just below the threshold for a small effect.
[d] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[e] Text is bolded to indicate that the strength of evidence has changed.
[f] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[g] Comparison was "usual care."
Text that is red indicates that a new study has been added. Color is used for visual emphasis only.
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased benefit; SOE: [✓] = low, [✓✓] = moderate, [✓✓✓] = high.

Table 7. Key Question 2: Harms of cannabinoids for chronic pain compared with placebo in the short term (4 weeks to <6 months)

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Comparable THC/CBD – Extracted, Oromucosal Spray	No effect (5) [✓]	No effect (3) [✓]	Large effect (6) [✓]	Moderate effect (6) [✓]	Large effect (6) [✓]
High THC – Synthetic or Purified, Oral	**Moderate effect (6, 1 new)[a]** [✓]	Insufficient (2, 1 new)	Large effect (4, 1 new) [✓✓]	**Large effect (4, 1 new)[a]** [✓]	Moderate effect (5, 1 new) [✓]
High THC – Extracted, Oral	Large effect (1) [✓]	Insufficient (1)	Large effect (1) [✓]	No evidence	No evidence
Low THC – Extracted CBD, Topical	No evidence	No evidence	No evidence	No evidence	No evidence

Product/THC to CBD Ratio	WAE Effect Size (N Studies) [SOE]	SAE Effect Size (N Studies) [SOE]	Dizziness Effect Size (N Studies) [SOE]	Nausea Effect Size (N Studies) [SOE]	Sedation Effect Size (N Studies) [SOE]
Low THC – Synthetic or Purified CBD, Oral[b]	Insufficient (4, 2 new)	Insufficient (2, 1 new)	**No effect (3, 2 new)[a]** [✓]	**Insufficient (2 new)[a]**	**No effect (3, 2 new)[a]** [✓]
Low THC – Synthetic CBD plus Purified THC, Oral[c]	**Insufficient (2, 1 new)[a]**	**Insufficient (2, 1 new)[a]**	**Potential effect (2, 1 new)[a, d]** [✓]	**Large effect (2, 1 new)[a]** [✓✓]	**Potential effect (2, 1 new) [a, d]** [✓]
Low THC – Sublingual CBD/THC, Extracted	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Low THC – Intraoral (topical) CBD, Unclear if Synthetic or Plant-derived)	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – CBDV, Oral	Insufficient (1)	Insufficient (1)	No evidence	No evidence	No evidence
Whole-Plant Cannabis (12% THC)[e]	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)	Insufficient (1)
Other cannabinoids – Hemp Seed Oil, Topical	No evidence	No evidence	No evidence	No evidence	No evidence
Other Cannabinoids – THC;CBD:CBN, Topical	No evidence	No evidence	No evidence	No evidence	No evidence

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.
[a] Text is bolded to indicate that the strength of evidence has changed.
[b] Low THC – Synthetic or Purified, Oral is a new meta-analysis category which includes two new trials and two previously included trials.
[c] Low THC – Synthetic CBD plus Purified THC, Oral is a new meta-analysis category based on one new and one previously included trial.
[d] Potential effect: SOE of low or higher; findings indicate at least a small magnitude of effect but not statistically significant.
[e] Comparison was "usual care."
Text that is red indicates that a new study has been added. Color is used for visual emphasis only.
Effect size: None (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk; SOE: [✓] = low, [✓✓] = moderate, [✓✓✓] = high.

4.2 Strengths and Limitations

The evidence base on cannabis and other plant-based treatments for chronic and subacute pain has multiple important limitations. Forty-eight percent of trials enrolled patients with chronic pain due to a neuropathic cause (7 in patients with multiple sclerosis, 7 with a mix of conditions or not specified, 3 with diabetic neuropathy, and 1 each with chemotherapy, HIV, back pain, or spinal cord injury). There is little or no evidence on other types of chronic pain, including low back pain, osteoarthritis, fibromyalgia, and inflammatory arthritis. Although inclusion criteria were revised to also address subacute pain, no eligible studies were identified. In terms of age, there is limited evidence on younger and older populations, with most patients

being middle-aged (mean age 53 years). Inclusion criteria were expanded in 2023 to include adolescents; however, no eligible studies have identified. Studies generally excluded patients with a history of psychiatric disorders other than prior history of depression or anxiety. Importantly, there was either no evidence or inadequate evidence to evaluate important patient populations based on sex/gender, race/ethnicity, age, or pregnancy/lactating status.

Another limitation is the lack of consistent nomenclature and details regarding the interventions and products studied. For example, products are described as plant-derived in some studies, but without a consistent way of describing the process or the resulting purity of the products. Other studies used words such as "standardized" to describe the amount of THC in a whole-plant cannabis product, again with lack of description of how this was defined or determined. Some observational studies did not describe specific cannabis products or categories evaluated; although such studies were included in the original review and initial updates they were excluded from subsequent updates, given the marked variability of cannabis products and potential impacts on outcomes. Studies that evaluated products that contained THC and CBD did not consistently report the ratio of THC to CBD, other than for Sativex oromucosal spray (close to a 1 to 1 ratio). Two trials that evaluated topical product did not describe details regarding extraction methods or product purity, and it was unclear if the products were intended to provide local or systemic effects.[89,90] When necessary, we attempted to obtain additional details regarding products from study authors; however, not all authors responded to queries. Although we attempted to categorize products accurately, some misclassification is possible. Other limitations include the absence of evidence on other plant-based compounds such as kratom, no RCT evidence on whole-plant cannabis products, and insufficient evidence for topical or sublingual CBD and cannabinoids other than THC or CBD due to small numbers of studies and methodological limitations.

Change in pain severity was the most commonly reported outcome, although there was some variability in how studies reported pain scores. Most studies collected current pain scores at baseline and at pre-specified time points (including the end of treatment), and other studies averaged daily pain scores over some period (e.g. 7 days). There was also variability in the pain scales used and how pain was characterized (e.g., average pain, worst pain, pain with activity, pain at rest). Although these measures are generally correlated, we focused on current pain at pre-specified time points when available to reduce heterogeneity in pain measures. Other important outcomes were mainly not reported or inconsistently reported or defined. Pain response, defined as a 30 percent or greater improvement in pain, was reported in 10 of 44 studies (23%); 25 of 44 studies (57%) reported on overall function (including pain interference) or disability. The studies poorly reported baseline use of opioids for pain, and only observational studies (7 studies) reported the impact of cannabis interventions on changes to prescription opioid use. While almost all studies reported the number of patients who withdrew from studies due to adverse events, 50 percent did not report SAEs, and 55 percent did not report the overall adverse events, particularly by group. SAEs were variably or poorly defined. Evidence for adverse events that have been reported in noncomparative observational studies and that were were prioritized for this review (development or exacerbation of psychosis, CUD, and cognitive deficits) was not available.

Other limitations were related to study design and small sample sizes (range 5 to 339; mean 87), particularly for assessing harms. The SOE of the findings was commonly downgraded due to imprecise estimates (see Appendix G). There were also differences in some key baseline characteristics, including baseline pain scores, which were frequently not adjusted for in study

analyses. Study durations of included RCTs were primarily short-term and included less than 6 months followup (1 RCT reported intermediate followup durations of 47 weeks); 41 percent of trials were 4 to 6 weeks long. This is a key limitation, chronic pain may fluctuate and can be influenced temporarily by an intervention or treatment; given the persistent nature of the pain the enduring impact of a treatment is most relevant. Similarly, adverse events such as CUD, cognitive deficits, and SAEs may take time to develop and are relatively uncommon, and longer and larger studies are required to capture such events. Two RCTs[67,81] utilized an enriched enrollment randomized withdrawal design in which all patients receive cannabis in a run-in phase; in this study design, only patients who respond to cannabis and tolerate it are randomized, to continuation or withdrawal. Such trials are intentionally designed to select for patients who respond to and tolerate cannabis, potentially exaggerating treatment effects and underestimating harms compared to patients not selected based on these features.[118,119] However, our findings were similar when the enriched enrollment randomized withdrawal trials were excluded from analyses. Well-designed head to head studies comparing a plant-based product with a standard of care treatment for chronic pain are lacking. The current evidence primarily consists of small, poorly designed, crossover or observational studies. We did not address potential impacts of cannabis as part of broader treatment models for chronic pain, such as impact on adherence to nonpharmacological therapy such as exercise or cognitive behavioral therapy or on managing polypharmacy.

Despite limitations in the evidence base, our review has several strengths. First, the living systematic review approach allowed us to add new studies soon after they are published, thereby providing an opportunity to update conclusions in a timely fashion. This approach may be particularly useful as cannabis and other plant-based treatments become more readily available to patients, clinicians, and researchers. Another strength of our approach was use of a framework that categorized cannabis-related products by both their THC and CBD ratios and type (synthetic or purified and extracted), providing a way to organize the evidence based on these two prominent cannabinoids consistent with how they are available to consumers. These categories were determined *a priori,* with the input of a Technical Expert Panel convened for this review. A final strength that separated this review from others was the exclusion of very short-term studies (e.g., a small number of dosing sessions), improving the applicability of findings to chronic pain, where use is likely to be longer term and symptoms are typically persistent.

There were also some limitations to our review process. We excluded non-English language publications and studies published only as abstracts. For almost all analyses, there were too few trials to apply graphical or statistical methods to detect small sample effects,[120] a marker of potential publication bias. Although there was a sufficient number of trials when combining synthetic or purified and extracted high THC to CBD ratio products versus placebo to apply such methods, which indicated potential small sample effects, results are difficult to interpret because the p-value for small sample effects was above the threshold for statistical significance, and potential heterogeneity was introduced by combining synthetic and extracted products. We did not identify unpublished trials of high THC to CBD products; one unpublished trial[121] of patients with diabetic neuropathy (n=294) found no difference between nabiximols (comparable THC to CBD ratio oromucosal spray) for diabetic neuropathy (0 to 10 scale, mean difference -0.12, 95% CI -0.60 to 0.36), suggesting that additional unpublished trials could attenuate estimates of effect.

Another potential limitation is that we categorized nabilone as a synthetic high-THC product, although it may be more accurately described as a chemical analog to THC, which could have

differing effects than THC/dronabinol. To address this possibility, we performed stratified analyses among outcomes that were pooled for synthetic high-THC interventions. Although the effect size for change in pain severity was larger with nabilone than with dronabinol, the difference between the cannabis products was not statistically significant. We also grouped purified THC (dronabinol) or CBD with synthetic dronabinol and CBD, because they are chemically identical to the synthetic product. As noted above, when synthetic THC was analyzed separately from purified THC, benefits were present with synthetic THC but not with purified THC. However, results should be interpreted with caution because they are not based on head-to-head comparisons, and there were potential sources of heterogeneity that could invalidate indirect comparisons. For example, all trials of purified THC evaluated dronabinol, but almost all trials of synthetic THC evaluated nabilone.Our meta-analyses were based on relatively small numbers of trials, which can result in overly narrow estimates using standard random effects approaches, including the profile likelihood model.[122,123] Therefore, we conducted sensitivity analyses using the Bartlett's correction. Although the Bartlett's correction resulted in wider CIs for pooled estimates, it did not change overall conclusions regarding the statistical significance of findings. The exception was high-THC products and increased risk of sedation, which was imprecise and no longer statistically significant using the Bartlett's correction. We did not apply the Bartlett's correction when there were fewer than five studies, because it may result in overly conservative (wide) CIs in this situation.[57] Meta-analyses based on fewer than five studies should be interpreted with caution, as CIs based on the profile likelihood method may be overly precise.

Our inclusion criteria required that the study population have chronic or subacute pain, or have subgroup analyses for this group, which may be why we did not find evidence related to kratom. As in other recent systematic reviews of interventions to treat chronic pain, we categorized the magnitude of effects as small, moderate, or large, in order to indicate the relative size of the effect, rather than according to published minimal clinically important difference (MCID) thresholds. Defining clinical significance in chronic pain is difficult because it is subjective and difficult to correlate with real-life experiences of patients. For example, the MCID for improvement in pain is 15 points on a 0 to 100 scale.[124] However, interventions commonly used for chronic pain, including opioids and nonsteroidal anti-inflammatory drugs do not achieve this level of reduction.[25,27] The typical reduction with opioids, nonopioid medications, nonpharmacological interventions, and cannabinoids is small, 5 to 10 points and may be considered a clinically important effect by patients and clinicians. In addition, when the pooled estimate is close to a predefined effect size threshold, a relatively small change in pooled estimates can result in recategorization. For a prior update, for synthetic high THC to CBD ratio products versus placebo, the effect size for pain intensity was reclassified from moderate to small, based on the addition of one new trial that decreased the pooled estimate from −1.10 to −0.95, which could suggest a more substantial change in the estimate than actually observed. On the other hand, use of predefined thresholds provides consistency in classifying effect size. With more evidence, pooled estimates should become more stable and less likely to undergo recategorization.

Although our review was not restricted to RCTs, we excluded uncontrolled and qualitative studies, as detailed in a companion white paper. Future reviews that include such studies could complement the quantitative approach focusing on controlled studies that we utilized.

4.3 Applicability

A number of factors could impact the applicability of our findings. The evidence currently is most applicable to patients with neuropathic pain with mostly moderate to severe pain (mean baseline score in RCTs was 6.5 on a 0 to 10 scale, with a range of 2.54 to 8.46). There was also considerable variability within the included studies with regard to the types of neuropathic pain, and treatment effects might be different depending on the specific neuropathic pain condition. As described above, two RCTs[67,81] utilized an enriched enrollment randomized trial design, which is purposefully designed to selectively randomize patients who respond to cannabis and tolerate it.

The evidence applies to adults with chronic pain, as there were no eligible studies of patients with subacute pain or adolescents. The evidence base addressed similar proportion of men and women, with around 60 percent of enrolled participants across all studies being female. While the age range across studies was broad, with mean study ranges of 24 to 68 years, the evidence is mainly applicable to middle-aged patients (overall mean age 53 years). The applicability of findings to older patients, in whom the balance of benefits to harms may be different, with potentially more harms, is uncertain. Non-White individuals were poorly represented in the studies. It is also unclear how the evidence applies to patients currently taking prescription opioids to treat chronic pain or patients with serious mental illness or other comorbidities, who are often excluded from trials. There was also insufficient information to determine how findings apply to patients with or without prior cannabis use, as no study stratified findings by prior cannabis use history and reporting of prior use was inconsistent. In terms of interventions, the evidence is most applicable to extracted comparable THC to CBD ratio oromucosal spray (nabiximols), high-THC (THC or THC analogue) synthetic and purified oral products (dronabinol or nabilone), and low-THC (CBD only) synthetic oral products. The evidence for comparable THC to CBD oral spray is applicable to mean dosing of 8.4 sprays per day (23 mg THC/21 mg CBD). The evidence for high THC to CBD ratio synthetic and plant-derived, synthetic equivalent products applies to dosing that was titrated upward, with a maximum dose of 13 to 25 mg per day of dronabinol and 0.25 to 4 mg per day of nabilone (mean doses not reported). For extracted high THC to CBD products, the evidence was too heterogeneous and limited (2 RCTs) to describe a generally applicable dose. For low THC to CBD products, findings are most applicable to oral synthetic CBD at a dose of up to 20 to 50 mg daily and combined oral purified THC and synthetic CBD (synthetic) at a dose of 22.5 to 25 mg THC and 45 to 50 mg CBD daily. The applicability of evidence to other products including topical or sublingual low THC to CBD ratio products and whole plant cannabis is very low.

Another factor impacting applicability is that the availability of the studied cannabis products varies depending on regulatory and other factors. For example, purified THC (dronabinol) was manufactured in the Netherlands and Denmark and may be available in some European countries, but is not approved by the U.S. Food and Drug Administration (FDA) at this time. Nabiximols are manufactured and available in Canada and some European countries, but are not approved by the FDA. In the United States, multiple whole-plant CBD products are available, but their composition varies, none are FDA approved, and availability varies from state to state depending on laws regarding cannabis use. Although our intervention categories were based on THC to CBD ratio and intended to group together interventions more likely to have similar effect, the generalizability of one cannabis product within a particular category to others is uncertain.

This evidence applies to short-term treatment and mainly informs the impact on mean changes in pain severity and common adverse events. Longer-term effects on these outcomes

may be different and important harms (e.g. psychosis, CUD, cognitive deficits) were not addressed in the short-term studies included in this review. Other information for assessing applicability, such as patient recruitment settings or the number randomized relative to the number eligible, was lacking.

Only 11 percent of studies were conducted in the United States, with the majority of studies conducted in from Europe (55%). We were unable to assess how the study country or other geographic location characteristics (e.g., rural, metropolitan) impacted the applicability of specific results.

A number of evidence gaps or limitations in the evidence potentially impacted the applicability of our findings including lack of evidence on extracted whole-plant or purified products, whole-plant cannabis, low THC to CBD ratio nonoral products, and kratom.

4.4 Implications for Clinical Practice, Education, Research, or Health Policy

The implications of the present findings for clinical practice and policy are mixed. Our results suggest that select individuals with chronic neuropathic pain may experience small short-term improvements in pain when using high THC to CBD cannabis products (synthetic or plant-derived, synthetic equivalent THC). The impact of this intervention on moderate or long-term outcomes is unknown. Extracted cannabis products with a comparable THC to CBD ratio may also result in small improvements in pain severity. On the other hand, cannabis products with a low THC to CBD ratio (oral synthetic or purified CBD alone or combined purified THC and synthetic CBD in a ratio of ~1:2) may not result in improvements in pain or function. Those who take products containing comparable or high ratios of THC or combined THC plus CBD in a ~1:2 ratio are also at increased risk for adverse events, including dizziness, sedation and nausea. Although relatively modest, the expected benefit of cannabis products compared to placebo appears comparable to those observed with prescription opioids, several nonopioid medications, and nonpharmacological interventions.[25,27,28] However, comparing effects of different interventions based on cross-trial comparisons must be done with extreme caution, due to potential differences across studies in the populations studied, interventions evaluated, and outcomes assessed; head-to-head trials are needed to better understand the comparative effectiveness of cannabis products versus other interventions. The evidence on adverse events with cannabis-related products is much less robust than the evidence on similar outcomes with opioids or nonopioid medications. The risk of sedation and dizziness appears similar with cannabis-related products, opioids, and the anticonvulsants pregabalin and gabapentin, while the risk for nausea may be larger with opioids and the antidepressant duloxetine than with cannabis-related products. However, these comparisons are qualitative and indirect and based on limited evidence on cannabis products relative to the other drugs and require confirmation. Evidence is too limited to compare effects on serious and long-term harms, even indirectly, though respiratory depressant effects of opioids potentially resulting in overdose and death are well-known. Understanding how cannabis products' adverse event profiles compare with other available treatments for chronic pain, particularly opioid and nonopioid medications, is essential to determine the comparative benefit to harm ratio of such treatments. At this time, the strength of this evidence is mostly low, and more data are needed to confidently recommend this as a treatment for various chronic pain-related conditions or for patients with diverse demographic or clinical characteristics. As multimodal approaches have been suggested for optimal treatment of chronic pain, cannabis may best be used as part of multimodal therapy. However, available

evidence was not designed to evaluate the effectiveness of or optimal components of multimodal therapy. No studies are available to inform decisions regarding use of cannabis for subacute pain or in adolescents.

As noted in the limitations above, baseline use of opioids for pain and the impact of cannabinoids on the use of opioids for pain were very poorly reported. In an effort to more effectively and safely manage chronic pain, a prominent goal of current research is to identify alternative treatments with equal or better benefits for pain while avoiding potential unintended consequences that could result in harms. Unfortunately, much of the findings to date are low SOE or insufficient evidence, and more high-quality studies are needed. Furthermore, the unavailability or unclear availability of studied cannabis products in specific settings may reduce the generalizability of findings.

Our synthesis of the evidence also suggests several important additional questions that might be suitable to be addressed in a clinical practice guideline, based on an assessment of potential benefits and harms, as well as uncertainties in the evidence. Examples of questions that could be addressed through a guideline process include: At what point in the treatment decision tree should cannabis-based medicines be considered? How should patient preferences be taken into account? What are pragmatic dosing guidelines? How should cannabis be used as part of multimodal therapy? To further inform guidelines, additional studies on the comparative effects on costs of care would be useful.

4.5 Implications for Future Research

The gaps in the research evidence that are outlined above lead to specific recommendations for conducting future studies that will improve the strength of the conclusions that can be drawn, and provide better guidance for policymakers, clinicians and patients alike. These are summarized in Table 8.

Table 8. Future research needs for cannabis and other plant-based treatments for chronic or subacute pain

PICOTS Element	Gap in Evidence	Suggested Future Research
Populations	• Non-White populations, older adults • Pain conditions other than neuropathic pain • Subacute pain • Adolescents	• Studies to specifically recruit non-White participants to ensure appropriate representation and diversity in studied populations • Stratified analyses according to sex, including effects in pregnant and lactating individuals • Studies of patients with subacute pain • Studies of adolescents • Studies to assess effects based on age differences • Pain populations expanded to include patients with nonneuropathic chronic pain, specifically back pain, other musculoskeletal pain, and fibromyalgia

4. Discussion

PICOTS Element	Gap in Evidence	Suggested Future Research
Interventions	• Extracted high THC to CBD ratio • Comparable THC to CBD ratio formulations other than extracted oromucosal spray • Extracted and nonoral low THC to CBD ratio products, whole-plant cannabis, and other cannabinoids • Kratom	• Studies of extracted high- THC to CBD ratio products, with clear description of extraction or purification process and consistent nomenclature regarding the final product • Studies of extracted low THC to CBD ratio products, with clear description or extraction or purification processes and consistent nomenclature regarding the final product • Additional studies of CBDV, hemp seed oil, and products containing non-THC or CBD cannabinoids such as CBN • Studies to compare different routes of administration (e.g., oromucosal spray, oral oil, oral capsule, smoked, etc.) • Studies should include and compare standardized treatment plans • Head-to-head studies on effects of different cannabinoids, including cannabinoids within a THC to CBD ratio category (e.g., synthetic vs. purified THC) • Studies to asses kratom and/or other plant-based treatments
Comparators	• Head-to-head comparisons	• Studies comparing plant-based interventions with other plant-based treatments (including head-to-head comparisons of different cannabis-related products), opioids, nonopioid medications, or nonpharmacological interventions to evaluate active-control comparisons to provide direct evidence on comparative effectiveness
Outcomes	• Pain response (≥30% improvement in pain severity) • Overall function, quality of life • Depression, anxiety, sleep, opioid use • Adverse event outcomes	• Outcomes should be consistently defined and reported across studies; ideally utilizing core outcome sets developed for studies of treatments for chronic pain. • Future studies should include pain response, measures of overall function, and adverse events (overall, serious, and withdrawals due to adverse events at a minimum), in addition to changes in pain severity. • Patient-centered and patient-reported outcomes (e.g., quality of life, depression, anxiety, and sleep) should be measured using validated tools for diagnosis and measurement of change. • In addition to reporting on opioid use prior to study enrollment, future studies should report on use of opioids, and other pain medications, during the trial. In particular, there is a need for more information on possible opioid sparing effects of plant-based treatments. • Studies need to assess serious harms such as development of cannabis use disorder, psychosis, and cognitive deficits. Other adverse events (e.g. sexual dysfunction and oral, dental-related, or pulmonary adverse events from inhaled, buccal, or smoked products) may need to be studied as new data emerge.
Timing	• Limited evidence on studies >6 weeks in duration	• Considering the chronic nature of the conditions, studies should provide followup assessments at longer timepoints, e.g., ≥3, 6 or 12 months

PICOTS Element	Gap in Evidence	Suggested Future Research
Study Design	• RCTs and cohort studies with adequate sample sizes to evaluate all important outcomes • Cohort studies with adequate control for confounding, ascertainment of exposures and outcomes • RCT and cohort studies with low risk of bias	• All designs: o Studies with larger sample sizes to adequately power statistical analyses for key outcomes are needed across all interventions except the synthetic medications o Should be designed and powered *a priori* to conduct subgroup analyses on important factors such as race, age, sex, and type of product or dose where these are variable • Cohort studies: o Should be conducted prospectively where possible, and conduct and report on ascertainment and validation of exposure and outcomes following best-practice guidance[102] o Should use appropriate methods to control for confounding on prognostic factors (e.g., baseline pain, prior and continued use of other interventions for pain, psychiatric illnesses) • RCTs: o Should not use run-in periods, or enriched enrollment randomized withdrawal designs that may overestimate effects and limit the generalizability of the findings[125] o Should be conducted using the parallel design (not crossover) • Systematic Reviews o As more evidence emerges, analyses should stratify and conduct subgroup analyses based on product specifics, pain conditions, and population characteristics.

Abbreviations: CBD = cannabidiol; CBDV = cannabidivarin; CBN = cannabinol; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; THC = tetrahydrocannabinol.

4.6 Conclusions

Low to moderate strength evidence suggests small improvements in pain (mostly neuropathic), and moderate to large increases in common adverse events (dizziness, sedation, nausea) with extracted comparable THC to CBD ratio and synthetic or purified high THC to CBD ratio products versus placebo during short-term treatment (1 to 6 months). Low to moderate strength evidence suggests that low THC to CBD ratio products (synthetic or purified CBD alone, or purified THC in combination with synthetic CBD) may not be associated with improved outcomes versus placebo. Evidence for whole-plant cannabis, other comparisons, other outcomes, and plant-based compounds was unavailable or insufficient to draw conclusions. No study evaluated adolescents or cannabis for subacute pain. Imprecision, lack of evidence for moderate and long-term outcomes and other key outcomes, such as SAEs and impact on opioid use during treatment, highlight the need for more research.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ANCOVA	analysis of covariance
BPI-SF	Brief Pain Inventory – Short Form
CBC	cannabichromene
CBD	cannabidiol
CBDV	cannabidivarin
CBG	cannabigerol
CBN	cannabinol
CI	confidence interval
CUD	cannabis use disorder
DAS28	28-Joint Disease Activity Scale
EPC	Evidence-based Practice Center
EQ-5D	EuroQol-5 Dimension
FDA	U.S. Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FM	fibromyalgia
GHQ-12	Short General Health Questionnaire
GNDS	Guy's Neurological Disability Scale
HADS-D	Hospital Anxiety and Depression Scale
IA	inflammatory arthritis
KQ	Key Question
LAO	long acting opioid
MCID	minimal clinically important difference
MCP	New Mexico Medical Cannabis Program
MD	mean difference
MME	morphine milligram equivalents
MS	multiple sclerosis
NA	not applicable
NPP	neuropathic pain
NR	not reported
NRS	numerical rating scale
ODI	Oswestry Disability Index
OME	oral morphine equivalent
OR	odds ratio
PBC	plant-based compound
PDI	Pain Disability Index

PICOTS	populations, interventions, comparators, outcomes, timing, and settings
PL	profile likelihood
RA	rheumatoid arthritis
RCT	randomized controlled trial
RDQ	Roland-Morris Disability Questionnaire
ROB	risk of bias
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEADS	Supplemental Evidence and Data for Systematic review
SF-36	Short Form-36
SMD	standardized mean difference
SOE	strength of evidence
SRDR+	Systematic Review Data Repository Plus
THC	tetrahydrocannabinol
TOO	Task Order Officer
VAS	visual analogue scale
VP	visceral pain
WAE	withdrawal due to adverse events
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WP	whole plant

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) ALL

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 chronic or subacute* or sub-acute*).ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute) adj3 pain).ti,ab,kw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 Medical Marijuana/
12 Mitragyna/
13 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,kf.
14 or/9-13
15 8 and 14
16 limit 15 to english language
17 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
18 ((animal or animals or avian or bird or birds or bovine or canine or cow* or dog or dogs or cat or cats or feline or hamster* or horse* or lamb or lamb* or mouse or mice or monkey or monkeys or murine or pig or piglet* or pigs or porcine or primate* or rabbit* or rat or rats or rodent* or songbird* or veterinar*) not (human* or patient*)).ti,kf,jw.
19 or/17-18
20 16 not 19

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 (chronic or subacute* or sub-acute*).ti,ab,kw.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute*) adj3 pain).ti,ab,hw.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,hw.
8 1 or 2 or 5 or 6 or 7

9 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab,hw.
10 8 and 9
11 conference abstract.pt.
12 "journal: conference abstract".pt.
13 "journal: conference review".pt.
14 "http://.www.who.int/trialsearch*".so.
15 "https://clinicaltrials.gov*".so.
16 11 or 12 or 13 or 14 or 15
17 10 not 16

Database: APA PsycInfo
1 Chronic Pain/
2 exp arthralgia/ or exp back pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3 Pain/
4 (chronic or subacute* or sub-acute*).ti,ab.
5 3 and 4
6 ((chronic or persistent or intractable or refractory or subacute* or sub-acute*) adj3 pain).ti,ab.
7 (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
8 1 or 2 or 5 or 6 or 7
9 Cannabis/
10 exp Cannabinoids/
11 (cannabis or cannabinoid* or cannabinol or marijuana or cannabidiol or phytocannabinoid* or tetrahydrocannabinol or dronabinol or nabilone or sativex or "CBD" or "THC" or kratom or khat or qat or psilocybin or hemp or hydroxymitragynine).ti,ab.
12 or/9-11
13 8 and 12
14 limit 13 to english language

Database: Elsevier Embase
('cannabis'/exp OR cannabis OR cannabinoid* OR 'cannabinol'/exp OR cannabinol OR 'marijuana'/exp OR marijuana OR 'cannabidiol'/exp OR cannabidiol OR phytocannabinoid* OR 'tetrahydrocannabinol'/exp OR tetrahydrocannabinol OR 'dronabinol'/exp OR dronabinol OR 'nabilone'/exp OR nabilone OR 'sativex'/exp OR sativex OR 'cbd' OR 'thc' OR 'kratom'/exp OR kratom OR 'khat'/exp OR khat OR 'qat'/exp OR qat OR 'psilocybin'/exp OR psilocybin OR 'hemp'/exp OR hemp OR hydroxymitragynine) AND ('chronic pain'/exp OR 'subacute pain'/exp OR 'subacute pain' OR arthralgia OR 'back pain' OR headache OR 'musculoskeletal pain' OR 'neck pain' OR neuralgia OR 'nociceptive pain' OR 'intractable pain' OR fibromyalgia OR myalgia OR arthritis OR osteoarthrtis) NOT ((animal OR animals OR avian OR bird OR birds OR bovine OR canine OR cow* OR dog OR dogs OR cat OR cats OR feline OR hamster* OR horse* OR lamb OR lamb* OR mouse OR mice OR monkey OR monkeys OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR songbird* OR veterinar*) NOT (human* OR patient*)) AND ('article'/it OR 'article in press'/it

OR 'conference paper'/it OR 'preprint'/it OR 'review'/it) AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: Elsevier Scopus

((TITLE (
cannabis OR cannabinoid* OR cannabinol OR marijuana OR cannabidiol OR phytocannabinoid* OR tetrahydrocannabinol OR dronabinol OR nabilone OR sativex OR "CBD" OR "THC" OR kratom OR khat OR qat OR psilocybin OR hemp OR hydroxymitragynine)) AND (TITLE ("chronic pain" OR "subacute pain" OR arthralgia OR "back pain" OR headache OR "musculoskeletal pain" OR "neck pain" OR neuralgia OR "nociceptive pain" OR "intractable pain" OR fibromyalgia OR myalgia OR arthritis OR osteoarthritis OR "neuropathic pain"))) AND NOT (TITLE-ABS-KEY (
animal OR animals OR avian OR bird OR birds OR bovine OR canine OR cow* OR dog OR dogs OR cat OR cats OR feline OR hamster* OR horse* OR lamb OR lamb* OR mouse OR mice OR monkey OR monkeys OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR songbird* OR veterinar*)) AND (LIMIT-TO (LANGUAGE , "English"))

Appendix B. Methods

Inclusion and Exclusion Criteria

Table B-1 outlines the inclusion and exclusion criteria related to populations, interventions, comparators, outcomes, timing, and settings (PICOTS), and study designs of interest for each Key Question. In the winter of 2022, the protocol was amended to include adolescents and subacute pain.[1] These changes were documented on in a revised protocol submitted to PROSPERO,[2] the Agency for Healthcare Research and Quality (AHRQ) Protocol, and the title, Key Questions, and inclusion and exclusion criteria were edited to reflect said changes. The changes expanded inclusion criteria to include subacute pain and adolescents.

Key Question 1. In adults or adolescents with chronic or subacute pain, what are the benefits of cannabinoids for treatment of chronic or subacute pain?

Key Question 2. In adults or adolescents with chronic or subacute pain, what are the harms of cannabinoids for treatment of chronic or subacute pain?

Key Question 3. In adults or adolescents with chronic or subacute pain, what are the benefits of kratom or other plant-based substances for treatment of chronic or subacute pain?

Key Question 4. In adults or adolescents with chronic or subacute pain, what are the harms of kratom or other plant-based substances for treatment of chronic or subacute pain?

Table B-1. PICOTS

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**All KQs**: Adults or adolescents (including pregnant or breastfeeding women) with noncancer chronic (>12 weeks or pain persisting past the time for normal tissue healing) or subacute pain (pain lasting 4 weeks to 3 months). See categorization of specifically included pain populations below.	**All KQs:** Children; adults with acute pain; patients at end of life or in palliative care (e.g., with late stage cancer-related pain)
Interventions	**KQs 1 and 2:** Cannabinoids (including synthetics) using different delivery mechanisms such as oral, buccal, inhalational, topical, or other administration routes **KQs 3 and 4:** Kratom or other plant-based substances; co-use of kratom or other plant-based substances and opioids **All KQs**: Co-use of other drugs for pain	**All KQs:** Non-plant-based interventions, capsaicin, herbal supplements
Comparators	**All KQs:** Any comparator, or usual care	**All KQs:** No comparison

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Outcomes	**All KQs:** Primary efficacy outcomes (i.e., pain, general function [e.g., Short-Form 36 Physical Functioning Scale] or pain-related [e.g., Oswestry Disability Index or Roland-Morris Disability Questionnaire, for low back pain] or disability, including pain interference[a]); harms and adverse effects (e.g., dizziness, nausea, sedation, development of cannabis use disorder, serious adverse events as defined by study); secondary outcomes (i.e., psychological distress including depression and anxiety, quality of life, opioid use, sleep quality, sleep disturbance, healthcare utilization)	**All KQs:** Other outcomes
Time of followup	**All KQs:** short term (4 weeks to <6 months), intermediate term (6 to <12 months), long term (≥1 year)	**All KQs:** studies with <1-month (4 weeks) of treatment or followup after treatment
Setting	**All KQs:** Any nonhospital setting or setting of self-directed care	**All KQs**: Hospital care, hospice care, emergency department care
Study design	**All KQs:** RCTs; observational studies with a concurrent control group for harms, and to fill gaps in the evidence for benefits	**All KQs:** Other study designs

Abbreviations: KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial.

[a] The degree to which pain directly interferes with patients' ability to participate in their daily activities (challenges in performing daily, social, or work-related tasks due to pain).

Important subgroups to consider in evaluating this evidence are:

- Specific types of pain: neuropathic pain (including nociceptive and centralized; patients with multiple sclerosis and painful skin disorders are included in this category), musculoskeletal pain (including low-back pain), visceral pain, fibromyalgia, inflammatory arthritis, headache disorders, sickle cell disease, and cancer pain (non-end of life)
- Degree of nociplasticity/central sensitization
- Patient demographics (e.g., age, race, ethnicity, sex, socioeconomic status)
- Comorbidities, including past or current substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder)
- Plant-based compound characteristics: route of administration, frequency of administration, potency of product, dose or estimated dose, specific compounds (e.g. tetrahydrocannabinol, cannabidiol, terpenes, flavonoids), and specific formulations used
- Co-use of other interventions for pain: opioids, nonopioids (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin, pregabalin)

Below are additional details on the scope of this project:

Study Design: For all Key Questions, we included randomized controlled trials (RCTs) of at least 4 weeks duration. We included observational studies for both benefits (to address gaps in evidence where RCTs are not available) and harms. Eligible observational studies must have assessed a mean duration of treatment of at least 4 weeks, and have concurrent controls (e.g., cohort and case-control studies). Those controlling for potential confounders were prioritized. As the evidence grew, and more RCTs became available throughout the project, we reassessed the need to include observational studies, specifically to address benefits and determined that due to the relatively small body of RCT evidence, we would continue to include observational studies

to supplement the evidence. When the RCT evidence on a given Key Question and outcome was insufficient, we included observational studies that met inclusion criteria. We did not exclude observational studies assessing harms. For all Key Questions, we excluded uncontrolled observational studies, case series, and case reports. Systematic reviews were used to supplement searches and identify primary studies.

Non-English Language Studies: We restricted to English-language articles, but reviewed English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria to help assess for the likelihood of language bias.

Study Selection

Electronic searches for evidence were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, the Cochrane Library, and SCOPUS® databases through April 28th, 2025. Searches were initially run in September 2020 with ongoing, automated monthly searches to identify newly published studies. For the 2023 update, search strategies were updated to include terms for subacute pain and applied to databases from inception to identify studies on subacute pain. No edits were needed to add adolescents, as there were previously no age restrictions in the strategies; however, a separate search was conducted from inception focused on adolescents and reviewed. Additionally, we re-assessed previously excluded studies for eligibility based on revised inclusion criteria. Search strategies are shown in Appendix A. Electronic searches were supplemented with review of reference lists of relevant studies and reviewing the two prior AHRQ pain reports[3,4] for studies that met our inclusion criteria. A Federal Register Notice was posted, and a Supplemental Evidence And Data for Systematic review (SEADS) portal was available for submission of unpublished studies for the original version of this report. As part of living systematic review methods, the electronic searches were automated to be run on a biweekly basis, with results emailed directly to the EPC librarian and the research team for processing. Citations were uploaded into DistillerSR® software for study selection management.

The updated criteria listed above were used to determine eligibility for inclusion and exclusion of abstracts. Following the second annual update, we excluded studies that did not report the specific cannabis products or categories used, due to potential variability in effects for different cannabis products. Using Distiller® SR, the review team conducted manual online assessment of study citations. All citations deemed potentially relevant by at least one of the reviewers were retrieved for full-text review. To ensure accuracy, any citation deemed not relevant for full-text review were reviewed by a second researcher. We initially planned to explore using the Distiller® AI feature to automate exclusion of abstracts that are clearly not relevant. Briefly, Distiller®SR AI is training in the background, learning from the human decisions on abstract eligibility. We planned to utilize the Distiller® AI decisions to assist with dual review when it reached a level of 95 percent accuracy (this typically takes 2,000 citations, but varies by topic).[5] However, the biweekly citation counts have been low, so the AI feature has not been required.

Data Extraction

After studies were selected for inclusion, data were abstracted into categories that included but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each Key Question as outlined in the previous inclusion and exclusion criteria section. Information

that was abstracted that was relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods, and characteristics of the population, intervention, and care settings. All study data were verified for accuracy and completeness by a second team member. On a quarterly basis, any newly identified studies were abstracted and evidence tables updated. Quarterly reports were published to the AHRQ website, and evidence tables are updated in AHRQ's Systematic Review Data Repository Plus (SRDR+).

Risk of Bias Assessment of Individual Studies

Predefined criteria were used to assess the risk of bias of individual controlled trials, systematic reviews, and observational studies. RCTs were evaluated using criteria and methods developed by the Cochrane Back Review Group,[6] and cohort and case-control studies were evaluated using criteria developed by the U.S. Preventive Services Task Force.[7] These criteria and methods were used in accordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews developed by AHRQ.[8] Studies were given an overall rating of "low," "medium," or "high" risk of bias. We used DistillerSR® software to conduct these assessments, using dual review by two independent reviewers. Disagreements identified by DistillerSR® were resolved through consensus. Assessments and final ratings were converted to evidence tables, and will be uploaded on a quarterly basis to SRDR+.

Data Synthesis and Analysis

We constructed evidence tables showing study characteristics (as discussed above), results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. Data were qualitatively summarized in tables, using ranges and descriptive analysis and interpretation of the results. Studies identified in prior AHRQ chronic pain reports[3,4] that meet inclusion criteria are included in this review. We evaluated the persistence of benefits or harms by evaluating the three periods identified in prior AHRQ pain reports (3 to <6 months, 6 to 12 months, and ≥12 months).[3,4,9-11]

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate.[12] The decision to conduct quantitative synthesis depends on presence of at least two studies, completeness of reported outcomes and a lack of heterogeneity among the reported results. To determine whether meta-analyses were indicated, we considered the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Meta-analyses were conducted using a random effects model based on the profile likelihood method,[13] and statistical heterogeneity was assessed using the I^2 method. Publication bias (small sample size bias) was assessed using funnel plots when there are eight or more studies in meta-analyses. To evaluate subgroup effects, we summarized within-study analyses of subgroup differences and performed study-level analyses on key demographic and clinical factors. Sensitivity analyses were conducted on study risk of bias.

The magnitude of effects for pain and function is classified using the same system used in other recent AHRQ Evidence-based Practice Center (EPC) reviews conducted on chronic pain[3,4,9-11] to provide a consistent benchmark for comparing results of pain interventions across reviews. Table B-2 provides thresholds for determining the magnitude of effect. A small effect is

defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point Visual Analog Scale (VAS), 0.5 to 1.0 points on a 0- to 10-point Numeric Rating Scale, or equivalent; for function as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect is defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large effects are defined as greater than moderate. We apply similar thresholds to other outcomes measures. Small effects using this system may be below published thresholds for clinically meaningful effects; however, there is variability across individual patients regarding what constitutes a clinically meaningful effect, which is influenced by several factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in pain or function using a treatment with low cost or no serious harms may be important.

Table B-2. Definitions of effect sizes

Effect Size	Definition
No effect/trivial effect	Below thresholds for small effect
Small effect	• MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	• MD >1 to 2 points on a 0 to10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	• MD >2 points on a 0 to10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

Abbreviations: MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference.

Findings that were not statistically significant were interpreted as follows:

- In determining the strength of evidence (SOE), the precision of evidence was downgraded two levels if inadequate sample size (optimal information size) *and* the 95% confidence interval includes both potentially meaningful benefit and harm (e.g. for a relative effect, the lower bound is ≤ 0.75 *and* the upper bound is ≥ 1.25)[14]
- If the magnitude of effect is below the threshold for a small effect, the finding is considered to have "No effect"[3]
- If the magnitude of effect is small or greater, and SOE is at least Low, the finding is considered to have a "Potential effect, not statistically significant"
- If the magnitude of effect is small or greater, and SOE is insufficient, the finding is considered to have "failed to demonstrate or exclude a beneficial/detrimental effect."[15]

Grading the Strength of the Body of Evidence

We assessed the SOE for all primary comparisons and outcomes listed in Table B-1. Regardless of whether evidence is synthesized quantitatively or qualitatively, the strength of evidence for each Key Question/body of evidence is initially assessed by one researcher for each clinical outcome by using the approach described in the AHRQ Methods Guide.[8] To ensure

consistency and validity of the evaluation, the strength of evidence is reviewed by the entire team of investigators prior to assigning a final grade on the following factors:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting/publication bias (suspected or undetected)

The SOE was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Plain-language statements are used in the Main Points, the Evidence Summary and the Discussion to convey the SOE. High SOE is described as "is associated with" or simply "reduces/increases;" moderate SOE is described as "probably;" and low SOE is described as "may be."[16]

Peer Review and Public Commentary

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Assessing Applicability

Applicability is assessed in accordance with the AHRQ Methods Guide,[17] which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of chronic pain patients with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities and may respond more poorly to treatment. Similarly, trials that use active run-in periods evaluate highly selected populations who tolerated and responded well to the study intervention, rather than the general population of chronic pain patients being considered for the intervention. Factors that may affect applicability which we have identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and psychiatric comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence, use of co-interventions), comparisons (e.g., type and dosing of comparison), outcomes (e.g., use of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, country), and study design features (e.g., use of run-in periods) relevant to applicability. We use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

Appendix B References

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Appendix C. Included Studies List

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Appendix D. Results – Study Level Summary Tables and Meta-Analyses

Appendix D-1. Individual Study Summary Tables

Tables D-1 through D-5 present details and results for primary outcomes, serious adverse events and withdrawals due to adverse events for each included study. Tables D-1 through D-3 provide information for randomized controlled trials and are organized by their respective ratio of tetrahydrocannabinol to cannabidiol. Table D-4 includes details for studies of other cannabinoids, and Table D-5 presents details of observational studies.

Table D-1. Comparable THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Blake, 2006 Moderate RCT Inflammatory arthritis-rheumatoid arthritis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 5.4 sprays/day (31) B: Placebo (27) 5 weeks Whole plant extracted	Pain severity (mean [SD NR] 0 to 10 NRS scale): 3.1 vs. 4.1, MD −1.04[b] (95% CI −1.9 to −0.18)	Function (mean [SD NR] 0 to 10 28−Joint Disease Activity Score scale): 5 vs. 5.9, MD −0.76[c] (95% CI −1.23 to −0.28)	SAE: 0/31 (0%) vs. 2/27 (7.41%), RR 0.18 (95% CI 0.01 to 3.49) WAE: 0/31 (0%) vs. 3/27 (11.11%), RR 0.13 (95% CI 0.01 to 2.32)
Langford, 2013 Low RCT Neuropathic pain- multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.8 sprays/day (167) B: Placebo (172) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 83/167 (49.75%) vs. 77/172 (44.77%), RR 1.11 (95% CI 0.89 to 1.39) Pain severity (mean [SD] 0 to 10 NRS scale): 4.54 (2.24) vs. 4.73 (2.26), MD −0.19 (SE 0.24) (95% CI −0.67 to 0.29)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.12, p=0.56 Function (0 to 100 SF−36 Physical Functioning scale): Treatment difference −0.45, p=0.785	WAE: 15/167 (8.98%) vs. 12/172 (6.98%), RR 1.29 (95% CI 0.62 to 2.67)
Lynch, 2014 High RCT (crossover) Neuropathic pain-chemotherapy induced	A: THC/CBD oromucosal spray (dose NR), mean dose 8 sprays/day (8) B: Placebo (8) 4 weeks Whole plant extracted	Pain severity (mean, 0 to 10 NRS−PI scale): 6 (95% CI 6.98 to 5.02) vs. 6.38 (95% CI5.67 to 7.09)	Function (mean [SD] 0 to 100 SF−36 Physical Functioning scale): 35.5 (9.19) vs. 46.5 (8.5), MD −11 (4.43) (95% CI −20.49 to −1.51)	SAE: 0/8 (0%) vs. 0/8 (0%), RR 1.00 (95% CI 0.02 to 45.13) WAE: 0/8 (0%) vs. 0/8 (0%), RR 1.00 (95% CI 0.02 to 45.13)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Nurmikko, 2007 Moderate RCT Neuropathic pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 10.9 sprays/day (63) B: Placebo (62) 5 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 16/73 (25.4%) vs. 9/62 (14.52%), RR 1.75 (95% CI 0.84 to 3.66) Pain severity (mean [SD NR] 0 to 10 NRS scale): 5.82 vs. 6.68, treatment difference −0.96 (95% CI −1.59 to −0.32)	Function (0 to 70 Pain Disability Index scale): MD −5.85 (95% CI −9.62 to −2.09)	SAE: 1/63 (1.6%) vs. 0/62 (0%), RR 2.95 (95% CI 0.12 to 71.13) WAE: 11/63 (17.46%) vs. 2/62 (3.23%), RR 5.41 (95% CI 1.25 to 23.43)
Rog, 2005 Moderate RCT Neuropathic pain- multiple sclerosis	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 9.6 sprays/day (34) B: Placebo (32) 5 weeks Whole plant extracted	Pain severity (mean [95% CI] 0 to 10 NRS scale): 3.85 (3.13 to 4.58) vs. 4.96 (4.19 to 5.72), treatment difference −1.25 (95% CI −2.11 to −0.39)	NR	SAE: 0/34 (0%) vs. 0/32 (0%), RR 0.94 (95% CI 0.02 to 46.16) WAE: 2/34 (5.88%) vs. 0/32 (0%), RR 4.71 (95% CI 0.23 to 94.58)
Selvarajah, 2010 High RCT Neuropathic pain- diabetic neuropathy	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 7 sprays/day[d] (15) B: Placebo (14) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 100 NPS scale): 51.6 (21.9) vs. 51.9 (24.1), MD −0.3 (SE 8.54) (95% CI −17.83 to 17.23)	Function (mean [SD] 0 to 100 SF−36 Physical Functioning scale): 30.5 (16.6) vs. 36.5 (27.9), MD 6 (SE 8.5) (95% CI −11.35 to 23.35)	NR
Serpell, 2014 Moderate RCT Neuropathic pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 8.9 sprays/day (128) B: Placebo (118) 15 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 34/123 (27.64%) vs. 19/117 (16.24%), RR 1.7 (95% CI 1.03 to 2.91) Pain severity (mean [SE NR] 0 to 10 NRS scale): Mean reduction −0.34 (0.23) (95% CI −0.79 to 0.11)	Pain interference (0 to 10 BPI−SF scale): Treatment difference −0.32 (SE 0.241) (95% CI −0.8 to 0.15)	SAE: 10/128 (7.81%) vs. 6% (7/118), RR 1.32 (95% CI 0.52 to 3.35) WAE: 25/128 (19.53%) vs. 25/118 (21.19%), RR 0.92 (95% CI 0.56 to 1.51)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
van Dam, 2024 Moderate RCT Fibromyalgia	A: 6.3% THC 8% CBD inhaled, vaporized cannabis, mean dose NR (29) B: Oxycodone 5 mg tablets, mean dose 15 mg/day (23) C: Combination inhaled cannabis and 5 mg oxycodone tablets, dose of cannabis NR, mean dose of oxycodone 10 mg/day (29) Purified	NR	NR	NR

Abbreviations: BPI−SF = Brief Pain Inventory−Short Form; CBD = cannabidiol; CI = confidence interval; MD = mean difference; NPS = Neuropathic Pain Scale; NR = not reported; NRS = Numeric Rating Scale; NRS−PI = Numeric Rating Scale for Pain Intensity; SAE = serious adverse events; SD = standard deviation; SE = standard error; SF−36 = Short Form−36; THC = tetrahydrocannabinol; RCT = randomized controlled trial; RR = relative risk; WAE = withdrawal due to due adverse events.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

[b] Difference in median differences.

[c] Difference in mean differences.

[d] Mean sprays calculated by systematic review team.

Table D-2. High THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Chaves, 2020 Low RCT Fibromyalgia	A: 1.2 mg THC/0.02 mg CBD sublingual drops, mean 3.6 drops/day (8) B: Placebo (9) 8 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 FIQ scale): 3.75 (2.49) vs. 7.67 (1.84), MD −3.92 (1.05) (95% CI −6.17 to −1.68)	Function (mean [SD] 0 to 10 FIQ scale): 5.83 (2.02) vs. 4.07 (2.25), MD 1.76 (1.04) (95% CI −0.46 to 3.98)	WAE: 0/8 (0%) vs. 0/9 (0%), RR 1.11 (95% CI 0.02 to 50.43)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
de Vries, 2017 Moderate RCT Visceral pain- chronic pancreatitis and postsurgical abdominal pain	A: THC oral tablet (Dronabinol), range 15 to 24 mg/day (30) B: Placebo (32) 7 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 2.4 (2.28) vs. 3.5 (2.42), MD −1.1 (SE 0.68) (95% CI −2.46 to 0.26)	NR	WAE: 7/30 (23.33%) vs. 2/32 (6.25%), RR 3.73 (95% CI 0.84 to 16.57)
Frank, 2008 Moderate RCT (crossover) Neuropathic pain	A: THC oral capsule (Nabilone), max dose 2 mg/day (48) B: Dihydrocodeine 30 mg, max dose 240 mg/day (48) 6 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): Treatment effect 5.7 (95% CI 0.5 to 10.9)	Function (mean [SD NR] 0 to 100 SF−36 Physical Functioning scale): Treatment effect 10.8 (95% CI 2.3 to 19.2)	SAE: 0/48 (0%) vs. 0/48 (0%), RR 1.00 (95% CI 0.02 to 49.40) WAE: 2/48 (4%) vs. 6/48 (12.5%), RR 0.34 (95% CI 0.07 to 1.57)
Hansen, 2023 Low RCT Neuropathic pain	A: THC 2.5 mg capsule (dronabinol), median dose 22.5 mg/day (32) B: Synthetic CBD 5 mg capsule, median dose 45 mg/day (31) C: CBD/THC capsule, median dose 35 mg synthetic CBD /17.5 mg THC (dronabinol)/day (31) D: Placebo (40)	Pain response ≥30% (NRS scale): 7/24 (29.2%) vs. 11/27 (40.7%) vs.14/28 (50%) vs.16/35 (45.7%), RR (95% CI) A vs. B: 0.72 (0.33 to 1.55) A vs. C: 0.58 (0.28 to 1.20) A vs. D: 0.64 (0.31 to 1.31) B vs. C: 0.81 (0.45 to 1.46) B vs. D: 0.89 (0.50 to 1.59) C vs. D: 1.09 (0.65 to 1.83) Pain severity change from baseline (mean [SDI] 0 to 10 NRS scale): −1.4 (2) vs. −1.4 (1.6) vs. −1.6 (1.8) vs. −1.8 (1.8)	NR	SAE: 2/32 (6.5%) vs. 0/31 (0%) vs. 0/31 (0%) vs. 2/40 (5%), RR (95% CI) A vs. B: 4.85 (0.24 to 97.11) A vs. C: 4.85 (0.24 to 97.11) A vs. D: 1.25 (0.18 to 8.39) B vs. C: 1.00 (0.02 to 48.87) B vs. D: 0.26 (0.013 to 5.15) C vs. D: 0.26 (0.013 to 5.15) WAE: 5/32 (15.6%) vs. 0/31 (0%) vs. 3/31 (9.7%) vs. 1/40 (2.5%), RR (95% CI) A vs. B: 10.67 (0.61 to 185.14) A vs. C: 1.61 (0.42 to 6.19) A vs. D: 6.25 (0.77 to 50.84) B vs. C: 0.14 (0.0077 to 2.65) B vs. D: 0.43 (0.018 to 10.14) C vs. D: 3.87 (0.42 to 35.43)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Pini, 2012 Low RCT (crossover) Headache- medication overuse headache	A: THC 0.5 mg oral capsule (Nabilone) daily (26) B: Ibuprofen 400 mg/day (26) 8 weeks Synthetic	Pain severity (mean [SD] 0 to 10 VAS scale): 5.55 (2.5) vs. 6.75 (2.4), MD −1.2 (0.68) (95% CI −2.57 to 0.17)	NR	WAE: 1/30 (3.33%) vs. 1/30 (3.33%), RR 1.00 (95% CI 0.66 to 15.26)
Rintala, 2010 High RCT (crossover) Neuropathic pain- spinal cord injury	A: THC 5 mg oral capsule (Dronabinol), max dose 20 mg/day (7) B: Diphenhydramine 25 mg, max dose 75 mg/day (5) 47 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 BPI scale): 5.8 vs. 5.8	NR	SAE: 1/7 (14.29%) vs. 1/5 (20%), RR 0.71 (95% CI 0.57 to 8.91) WAE: 1/7 (14.29%) vs. 0/5 (0%), RR 2.25 (95% CI 0.11 to 46.13)
Schimrigk, 2017 Low RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg oral capsule (Dronabinol), mean dose 13 mg/day (124) B: Placebo (116) 16 weeks Synthetic	Pain severity (mean [SD] 0 to 10 NRS scale): 4.48 (2.04) vs. 4.92 (2.04), MD NR, p=0.676	NR	SAE: 12/124 (9.68%) vs. 7/116 (6.03%), RR 1.53 (95% CI 0.63 to 3.76) WAE: 19/124 (15.32%) vs. 12/116 (10.34%), RR 1.48 (95% CI 0.75 to 2.91)
Skrabek, 2008 Moderate RCT Fibromyalgia	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 2 mg/day (15) B: Placebo (18) 4 weeks Synthetic	Pain severity (mean [SD NR] 0 to 10 VAS scale): 4.8 vs. 5.6, MD −1.43, p<0.05	NR	SAE: 0/15 (0%) vs. 0/18 (0%), RR 1.19 (95% CI 0.02 to 56.54) WAE: 1/20 (5%) vs. 1/20 (5%), RR 1.00 (95% CI 0.07 to 14.90)
Toth, 2012 Low RCT Neuropathic pain- diabetic neuropathy	A: THC 0.5 mg oral capsule (Nabilone), max dose 4 mg/day (13) B: Placebo (13) 5 weeks Synthetic	Pain response ≥30% (NRS scale): 11/13 (84.62%) vs. 5/13 (38.46%), RR 2.2 (95% CI 1.06 to 4.55) Pain severity (mean [SD] 0 to 10 NRS scale): 3.5 (1.3) vs. 5.4 (1.7), MD −1.9 (0.59) (95% CI −3.13 to −0.68)	Pain interference (mean [SD] 0 to 10 MBPI scale): 2.5 (1.6) vs. 3.6 (0.9), MD −1.1 (0.51) (95% CI −2.15 to −0.05)	NR
Turcotte, 2015 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), max dose 2 mg/day (8) B: Placebo (7) 9 weeks Synthetic	Pain severity (mean [SD NR] 0 to 100 VAS scale): 35 vs. 57[b]	Pain interference (mean [SD NR] 0 to 100 VAS impact scale): 41 vs. 40[b]	SAE: 0/8 (0%) vs. 0/7 (0%), RR 0.89 (95% CI 0.02 to 39.84) WAE: 1/8 (12.5%) vs. 0/7 (0%), RR 2.67 (95% CI 0.13 to 56.63)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Wissel, 2006 High RCT (crossover) Neuropathic pain- multiple sclerosis	A: THC 0.5 mg oral capsule (Nabilone), endpoint dose 1 mg/day (13) B: Placebo (13) 4 weeks Synthetic	Pain severity (median [SD NR] 11 Point Box Test): 4 vs. 6, p<0.05	NR	WAE: 2/13 (15.38%) vs. 0/13 (0%), RR 5.00 (95% CI 0.26 to 95.02)
Zajicek, 2012 Moderate RCT Neuropathic pain- multiple sclerosis	A: THC 2.5 mg capsule, max dose 25 mg/day (143) B: Placebo (134) 12 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 CRS scale): 4.1 (2.9) vs. 4.7 (3.0), MD −0.6 (95% CI −1.3 to 0.1)	NR	SAE: 7/143 (4.9%) vs. 3/134 (2.24%), RR 2.19 (95% CI 0.58 to 8.28) WAE: 30/143 (20.98%) vs. 9/134 (6.72%), RR 3.12 (95% CI 1.54 to 6.33)
Zubcevic, 2022 Low RCT Peripheral neuropathic pain	A: THC 2.5 mg capsule (dronabinol), max dose 25 mg/day (28) B: Synthetic CBD 5 mg capsule, max dose 50 mg/day (27) C: CBD/THC capsule, max dose 50 mg CBD/25 mg THC (dronabinol)/day (30) D: Placebo (30)	Pain response ≥30% (NRS scale): 12/28 (42.86%) vs. 9/27 (33.34%) vs. 18/30 (60.00%) vs. 17/30 (56/67%), RR (95% CI) A vs. B: 1.29 (0.65 to 2.55) A vs. C: 0.71 (0.43 to 1.20) A vs. D: 0.76 (0.45 to 1.28) B vs. C: 0.56 (0.30 to 1.02) B vs. D: 0.59 (0.32 to 1.09) C vs. D: 1.06 (0.69 to 1.62) Pain severity change from baseline (mean [95% CI] 0 to 10 NRS scale): −1.4 (-2.2 to -0.7) vs. -0.6 (-1.2 to 0.1) vs. -1.9 (-2.7 to -1.2) vs. -1.9 (-2.7 to -1.0)	Pain interference (mean [SD] 0 to 10 Pain Impact on Daily Activities Scale): MD (95% CI) A vs. D: 0.36 (-1.19 to 1.91) B vs. D: 1.24 (-0.32 to 2.81) C vs. D: 0.89 (-0.64 to 2.42)	SAE: 0/28 (0%) vs. 0/27 (0%) vs. 1/30 (3.3%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.96 (0.02 to 47.01) A vs. C: 0.36 (0.02 to 8.40) A vs. D: 1.07 (0.02 to 52.14) B vs. C: 0.37 (0.02 to 8.70) B vs. D: 1.11 (0.02 to 53.97) C vs. D: 3.00 (0.13 to 70.83) WAE: 1/28 (3.57%) vs. 2/27 (7.41%) vs. 4/30 (13.33%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.48 (0.05 to 5.01) A vs. C: 0.27 (0.03 to 2.25) A vs. D: 3.21 (0.14 to 75.62) B vs. C: 0.56 (0.11 to 2.80) B vs. D: 5.54 (0.28 to 110.42) C vs. D: 9.00 (0.51 to 160.18)

Abbreviations: BPI = Brief Pain Inventory; CBD = cannabidiol; CI = confidence interval; CRS = category rating scale; FIQ = Fibromyalgia Impact Questionnaire; MBPI = Modified Brief Pain Inventory; MD = mean difference; NR = not reported; NRS = Numeric Rating Scale; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; SE = standard error; THC = tetrahydrocannabinol; RR = relative risk; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

[b] Estimated from graph.

Table D-3. Low THC to CBD ratio study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Bassat, 2023 High RCT (crossover) Chronic pain-mixed	A: 3 drops (2.5 mg THC/15 mg CBD) sublingual oil, max dose 18 drops per day (15 mg THC/90 mg CBD) (7) B: 3 drops (2.5 mg THC/15 mg CBD) ≥97% purified sublingual oil, max dose 18 drops per day (15 mg THC/90 mg CBD) (5) C: Placebo (9) 16 weeks Whole plant extracted	NR	NR	SAE: 6/9 (67%) vs. 4/6 (67%) vs. 3/10 (30%) WAE: 1/4 (25%) vs. 1/5 (20%) vs. 1/6 (16.7%)
Hansen, 2023 Low RCT Neuropathic pain	A: THC 2.5 mg capsule (dronabinol), median dose 22.5 mg/day (32) B: Synthetic CBD 5 mg capsule, median dose 45 mg/day (31) C: CBD/THC capsule, median dose 35 mg synthetic CBD /17.5 mg THC (dronabinol)/day (31) D: Placebo (40)	Pain response ≥30% (NRS scale): 7/24 (29.2%) vs. 11/27 (40.7%) vs.14/28 (50%) vs.16/35 (45.7%), RR (95% CI) A vs. B: 0.72 (0.33 to 1.55) A vs. C: 0.58 (0.28 to 1.20) A vs. D: 0.64 (0.31 to 1.31) B vs. C: 0.81 (0.45 to 1.46) B vs. D: 0.89 (0.50 to 1.59) C vs. D: 1.09 (0.65 to 1.83) Pain severity change from baseline (mean [SDI] 0 to 10 NRS scale): −1.4 (2) vs. −1.4 (1.6) vs. −1.6 (1.8) vs. −1.8 (1.8)	NR	SAE: 2/32 (6.5%) vs. 0/31 (0%) vs. 0/31 (0%) vs. 2/40 (5%), RR (95% CI) A vs. B: 4.85 (0.24 to 97.11) A vs. C: 4.85 (0.24 to 97.11) A vs. D: 1.25 (0.18 to 8.39) B vs. C: 1.00 (0.02 to 48.87) B vs. D: 0.26 (0.013 to 5.15) C vs. D: 0.26 (0.013 to 5.15) WAE: 5/32 (15.6%) vs. 0/31 (0%) vs. 3/31 (9.7%) vs. 1/40 (2.5%), RR (95% CI) A vs. B: 10.67 (0.61 to 185.14) A vs. C: 1.61 (0.42 to 6.19) A vs. D: 6.25 (0.77 to 50.84) B vs. C: 0.14 (0.0077 to 2.65) B vs. D: 0.43 (0.018 to 10.14) C vs. D: 3.87 (0.42 to 35.43)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Pramhas, 2023 Moderate RCT Musculoskeletal – knee osteoarthritis	A: Purified CBD capsule (600 mg/day) (43) B: Placebo (43) 8 weeks Plant-derived	Pain severity change from baseline (mean [95% CI] 0 to 10 WOMAC Pain subscale): −2.5 (−3.3 to −1.8) vs. −2.4 (−3.2 to −1.7)	Physical Function change from baseline (mean [95% CI] 0 to 10 WOMAC scale): −1.5 (−2.4 to −0.7 vs. −1.7 (−2.5 to −0.8) SF-36 Physical Functioning change from baseline (mean [95% CI]): 8 (4.3 11.5) vs. 7.3 (4 to 10.7)	WAE: 9/43 (20.9%) vs. 6/43 (11.6%) RR: 1.5 (95% CI 0.58 to 3.84)
Vela, 2021 Moderate RCT Musculoskeletal - hand osteoarthritis and psoriatic arthritis	A: CBD oral tablet (20 to 30 mg/day) (68) B: Placebo (61) 12 weeks Synthetic CBD	Pain response ≥30% (VAS 0 to 100 scale): 27/68 (39.7%) vs. 24/61 (39.3%), RR 1.01 (95% CI 0.66 to 1.55) Pain severity (0 to 100 VAS scale): mean NR, MD 0.23 (95% CI −9.41 to 9.9)	Function/disability (0 to 3 HAQ-DI scale): mean NR, MD 0.03 (95% CI −0.11 to 0.18)	SAE: 2/58 (3.4%) vs. 2/61 (3.3%), RR 1.05 (95% CI 0.15 to 7.22) WAE: 0/70 (0%) vs. 2/66 (3%), RR 0.19 (95% CI 0.01 to 3.86)
Walczyńska-Dragon, 2024 Moderate RCT Temporomandibular disorders - Sleep bruxism and muscle-related temporomandibular disorders	A: CBD 10% gel (40 mg CBD/day) (20) B: CBD 5% gel (20% CBD/day) (20) C: Placebo (20) Unknown derivative	Pain severity change from baseline (median [interquartile range] 0 to 10 VAS scale): −5.6 (−2.4) vs. −2.5 (0.63) vs. −0.5 (1.03)	NR	NR
Xu, 2020 High RCT (crossover) Neuropathic pain- mixed	A: CBD cream (250 mg/3 oz) up to 4 times daily (15) B: Placebo (14) 4 weeks Whole plant extracted	Pain severity (mean [SD] 0 to 10 NPS scale): 3.33 (2.02) vs. 5.55 (2.81), MD −2.22 (95% CI −4.07 to −0.37)	NR	SAE: 0/15 (0%) vs. 0/14 (0%), RR 0.94 (95% CI 0.02 to 44.33)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Zubcevic, 2022 Low RCT Peripheral neuropathic pain	A: THC 2.5 mg capsule (dronabinol), max dose 25 mg/day (28) B: Synthetic CBD 5 mg capsule, max dose 50 mg/day (27) C: CBD/THC capsule, max dose 50 mg CBD/25 mg THC (dronabinol)/day (30) D: Placebo (30)	Pain response ≥30% (NRS scale): 12/28 (42.86%) vs. 9/27 (33.34%) vs. 18/30 (60.00%) vs. 17/30 (56/67%), RR (95% CI) A vs. B: 1.29 (0.65 to 2.55) A vs. C: 0.71 (0.43 to 1.20) A vs. D: 0.76 (0.45 to 1.28) B vs. C: 0.56 (0.30 to 1.02) B vs. D: 0.59 (0.32 to 1.09) C vs. D: 1.06 (0.69 to 1.62) Pain severity change from baseline (mean [95% CI] 0 to 10 NRS scale): −1.4 (-2.2 to -0.7) vs. -0.6 (-1.2 to 0.1) vs. -1.9 (-2.7 to -1.2) vs. -1.9 (-2.7 to -1.0)	Pain interference (mean [SD] 0 to 10 Pain Impact on Daily Activities Scale): MD (95% CI) A vs. D: 0.36 (-1.19 to 1.91) B vs. D: 1.24 (-0.32 to 2.81) C vs. D: 0.89 (-0.64 to 2.42)	SAE: 0/28 (0%) vs. 0/27 (0%) vs. 1/30 (3.3%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.96 (0.02 to 47.01) A vs. C: 0.36 (0.02 to 8.40) A vs. D: 1.07 (0.02 to 52.14) B vs. C: 0.37 (0.02 to 8.70) B vs. D: 1.11 (0.02 to 53.97) C vs. D: 3.00 (0.13 to 70.83) WAE: 1/28 (3.57%) vs. 2/27 (7.41%) vs. 4/30 (13.33%) vs. 0/30 (0%), RR (95% CI) A vs. B: 0.48 (0.05 to 5.01) A vs. C: 0.27 (0.03 to 2.25) A vs. D: 3.21 (0.14 to 75.62) B vs. C: 0.56 (0.11 to 2.80) B vs. D: 5.54 (0.28 to 110.42) C vs. D: 9.00 (0.51 to 160.18)

Abbreviations: CBD = cannabidiol; HAQ-DI = Health Assessment Questionnaire – Disability Index; MD = mean difference; NPS = Neuropathic Pain Scale; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SD = standard deviation; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to adverse event; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

Table D-4. Other cannabinoids study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events[a]
Abbasifard, 2024 Moderate RCT Knee osteoarthritis	A: Topical hemp seed oil (concentration NR), 10 drops per day (30) B: Diclofenac 1% gel, 10 drops daily (30) C: Placebo (30) Plant-derived	Pain severity (mean [SD] 1 to 10 VAS scale): 3.53 (0.78) vs. 3.37 (1.06) vs. 5.30 (0.75), MD −0.16 (95% CI −0.64 to 0.32) for A vs. B, 1.77 (95% CI 1.37 to 2.17) for A vs. C	Function (mean [SD] 0 to 120 WOMAC scale): 22.39 (4.44) vs. 21.23 (6.04) vs. 29.43 (6.75), MD −1.16 (95% CI −3.90 to 1.58) for A vs. B, 7.04 (95% CI 4.09 to 10.0) for A vs. C	None
Eibach, 2020 Moderate RCT (crossover) Neuropathic pain- HIV associated	A: CBDV oral solution (50 mg/mL) 400 mg/day (16) B: Placebo (16) 4 weeks Whole plant extracted	Pain response ≥30% (NRS scale): 6/16 (37.5%) vs. 13/16 (81.25%), RR 0.46 (95% CI 0.24 to 0.91) Pain severity (mean [SD] 0 to 10 NRS scale): 2.74 (1.47) vs. 3.67 (2.62), MD −0.62 (95% CI −0.27 to 1.51)	Pain interference (0 to 10 BPI−SF scale): MD −0.35 (95% CI −1.36 to 0.43)	SAE: 1/16 (6.25%) vs. 0/16 (0%), RR 3.00 (95% CI 0.13 to 68.57) WAE: 1/16 (6.25%) vs. 0/16 (0%), RR 3.00 (95% CI 0.13 to 68.57)
Seevathee, 2025 Moderate RCT Diabetic peripheral neuropathy	A: THC:CBD:CBN (3.20:0.32:0.65 mg/drop) topical oil, 1-2 drops per day for mild pain, 3-4 drops for moderate pain, 5-6 drops for severe pain (47) B: Placebo (46)	Pain severity (mean [SD] 0 to 120 NPSI-T scale): 5.57 (8.14) vs. 22.85 (11.97), MD 17.28 (95% CI 13.07 to 21.49)	NR	NR

Abbreviations: CBDV = cannabidivarin; CBN = cannabinol; MD = mean difference; NPSI-T = Neuropathic Pain Symptom Inventory- Thai version; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SD = standard deviation; WOMAC =Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Other serious adverse events (i.e., psychosis and cannabis use disorder) not reported in any study.

Table D-5. Observational study primary outcomes

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Bestard, 2011 Moderate Prospective cohort Neuropathic pain-mixed	A: THC oral capsule (Nabilone), mean dose 3.05 mg/day (49) B: Gabapentin, mean dose 2,295.5 mg/day (52) C: Gabapentin + THC capsule, mean dose NR + 3.02 mg/day (55) 6 months Synthetic	Pain intensity (mean [SD] 0 to 100 VAS scale): 28.0 (10.5) vs. 33.8 (11.6) vs. 33.1 (20.2), MD −5.8 (95% CI −10.18 to −1.42) for A vs. B, −5.1 (95% CI −11.48 to 1.28) for A vs. C	Pain interference (mean [SD] 0 to 10 BPI scale): 4.5 (2.3) vs. 4.6 (2.2) vs. 4.5 (2.2), MD −0.1 (95% CI −0.99 to 0.79) for A vs. B, 0.00 (95% CI −0.88 to 0.88) for A vs. C Function (mean [SD] 0 to 100 SF-36 scale): 48.3 (27.2) vs. 46.5 (25.1) vs. 43.7 (26.4), MD 1.80 (95% CI −8.53 to 12.13) for A vs. B, 4.60 (95% CI −5.83 to 15.03) for A vs. C	SAE: 0/49 (0%) vs. 0/52 (0%) vs. 0/55 (0%) A vs. B RR 1.06 (95% CI 0.21 to 52.41) B vs. C RR 1.06 (95% CI 0.02 to 52.30) A vs. C RR 1.12 (95% CI 0.02 to 55.41) WAE: 5/49 (10%) vs. 12/52 (23%) vs. 5/55 (9%) A vs. B RR 0.44 (95% CI 0.17 to 1.16) B vs. C RR 2.54 (95% CI 0.96 to 6.71) A vs. C RR 1.12 (95% CI 0.35 to 3.65)
Campbell, 2018 Moderate Prospective cohort Chronic non-cancer pain- mixed	A: Self-reported frequent cannabis use of ≥20 days/mo B: No cannabis use Overall N Baseline: 1,514 4-year followup: 1,217 Groups unclear 4 years Unclear THC concentration; patient-driven choice	A vs. B (reference) Pain intensity (Adjusted mean [SE]; BPI, 0-10 scale): 5.2 (0.14) vs. 4.9 (0.03); Beta: 0.37 (95% CI, −0.23 to 1.10), p=0.20	A vs. B Pain Interference (Adjusted mean [SE]; BPI pain interference, 0-10 scale): 5.2 (0.19) vs. 5.4 (0.04); Beta: −0.63 (95% CI, −1.46 to 0.19), p=0.13	NR
Giangregorio, 2024 Moderate Retrospective cohort Muscle, joint, or nerve pain	A: High THC (5:1 THC:CBD ratio or greater) B: Balanced THC:CBD less than 5:1 and greater than 1:5 THC:CBD ratio) C: High CBD (1:5 THC:CBD ratio or lower)	A vs. B Median reported change in NRS scores across treatment sessions: −3.0 (IQR −4.5 to −2.0)	NR	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Gruber, 2021 High Prospective cohort Mixed (primarily musculoskeletal)	A: THC/CBD: Medicinal cannabis program, mean dose THC 13.3 mg/day, CBD 28.9 mg/day (37) B: Usual care, dose NA (9) 12 weeks Mixed cannabis products	Pain intensity (mean [SD] 0 to 100 VAS scale): 34.07 (22.36) vs. 48.78 (30.42); MD −14.71 (95% CI, −32.71 to 3.29)	A vs. B Function (mean [SD], 0 to 10 PDI scale): 18.13 (12.26) vs. 19.22 (12.73); MD −1.09 (95% CI −10.33 to 8.16) SF-36 Function (mean [SD], 0 to 100 scale[a]): 70.00 (22.87) vs. 69.44 (26.98); MD 0.56 (95% CI −17.17 to 18.29)	NR
Halman, 2024 High Prospective cohort Mixed pain, mental health symptoms	A: Medical cannabis, THC dominant (7) B: Medical cannabis, CBD dominant (30) C: Medical cannabis, comparable ratio of THC to CBD (34) D: Medical cannabis, mixed (25)	NR	NR	NR
Holt, 2024 Moderate Retrospective cohort Mixed (arthritis, neurological, headaches, unspecified pain diagnoses)	A: Patients with chronic pain initiating medical cannabis (THC, THC:CBD, and CBD) during 2018-21 (5,391) B: Matched controls not initiating cannabis (26,941)	NR	NR	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Lee, 2021[b] Moderate Matched cohort NR	A: Chronic opioid users authorized to use medical cannabis in Canada (5,373) B: Controls who did not receive authorization for medical cannabis in Canada (5,373) 20 months Unknown THC concentration; patient-driven choice	NR	NR	NR
Merlin, 2019[b] High Prospective cohort Chronic non-cancer pain (HIV)	A: Daily or weekly use of marijuana (55) B: Monthly or 1-2 times a month use of marijuana (65) C: No use (313) 52 weeks Unknown THC concentration; patient-driven choice	NR	NR	NR
Schubert, 2023 High Prospective cohort Chronic refractory pain, including arthritis	A: CBD only (174) B: CBD dominant (two fold ratio increase in main cannabinoid) (37) C: Balanced (113) D: THC dominant (THC only) (27) Prescribed products were either oral liquids, capsules, flos, or granulate	Pain intensity, improved, n (%): 37 (21.3) vs. 8 (21.6) vs. 27 (23.9) vs. 5 (13.5)	Pain interference, improved, n (%): 64 (36.8) vs. 14 (37.8) vs. 49 (43.4) vs. 13 (35.1) Physical function, improved, n (%):57 (32.8) vs. 11 (29.7) vs. 40 (35.4) vs. 12 (32.4)	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Sridharan, 2024 High Prospective cohort Fibromyalgia	A: Prescribed cannabis, oil (77) B: Prescribed cannabis, dried flower (14) C: Prescribed cannabis, combination of oil and flower (57)	Mean change (SD) in fibromyalgia symptom improvement, 12 months: −1.16 vs. −1.86 vs. −2.23, p value for interaction = 0.365	NR	NR
Tait, 2023 Moderate Prospective cohort Chronic non-cancer pain	A: A. Cannabis-based sublingual/oral medium-chain triglyceride-based oil containing CBD and THC (348) B. Inhaled dried cannabis flower containing trace CBD and THC (36) C. A + B (377) Dried flower concentration: 20% THC, 0% (trace) CBD Cannabis-based oils ranged from all THC, all CBD, and ratios ranging from 1:1 to 1:20	A vs. B vs. C Pain, VAS score (scale 0-10; median, IQR) 1 month: 7.00 (5.00-8.00) vs. 5.50 (3.00-6.75) vs. 6.00 (5.00-7.75) 3 months: 6.00 (4.00-7.00) vs. 5.00 (3.00-7.00) vs. 6.00 (4.00-7.00) 6 months: 6.00 (3.00-7.25) vs. 3.00 (1.50-5.00) vs. 5.00 (3.00-7.00)	A vs. B. vs. C BPI-Interference score (scale 0-10; median, IQR) 1 month: 5.86 (3.64-7.36) vs. 5.14 (2.21-5.93) vs. 5.79 (3.57-7.43) 3 months: 5.29 (3.43-6.82) vs. 4.14 (2.43-6.29) vs. 5.00 (2.86-6.93) 6 months: 4.71 (3.14-6.43) vs. 2.14 (1.50-3.64) vs. 4.50 (2.64-6.64) Likelihood of improvement, adjusted OR A vs. B: 1.61 (95% CI 0.21 to 12.18); A vs. C: 1.90 (95% CI 0.68 to 5.29)	NR

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Ueberall, 2022a Moderate Retrospective cohort Peripheral neuropathic pain- mixed	A: Nabiximols as an add-on treatment; 16.6 (SD 6.5) mg THC/15.4 (SD 4.1) mg CBD/day (337) B: Dronabinol as an add-on treatment; 17.2 (SD 7.6) mg THC/day (337) 24 weeks Whole plant extracted and synthetic	A vs. B Pain intensity index (VAS 0-100 scale) mean relative change (improvement) rates at week 24 83.4% vs. 75.9%, p<0.001 Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 3.50 (95% CI 1.6 to 5.4)	A vs. B Pain-related disabilities (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): 76.0% vs. 68.3%, p<0.001	A vs. B WAE: 5.9% vs. 14.8%, RR 2.5, p<0.001
Ueberall, 2022b Moderate Retrospective cohort Peripheral neuropathic back pain- mixed	A: 2.7 mg THC/2.5 mg CBD/100 mcl oromucosal spray, mean dose 16.7 mg THC/15.5 mg CBD/day (655) B: Long-acting opioid, MME 69.4 mg/day 24 weeks Whole plant extracted and long-acting opioid	A vs. B Pain intensity index (mean relative change from baseline at week 24, 0 to 100 VAS scale): −72.3% (SD 30.5) vs. −49.2% (SD 39.9) Pain intensity index (VAS 0-100 scale, converted to 0-10) mean difference: 9.90 (95% CI 8.05 to 11.75)	A vs. B Pain-related disabilities (mean relative change [improvement] rates at week 24, 0 to 100 VAS scale): −66.1 (28.7) vs. −42.9 (34.5), p<0.001	WAE: 7.9% vs. 29.3%, RR 0.27 (95% CI 0.20 to 0.36)

Author, Year Risk of Bias Study Design Pain Condition	Comparison (n) Followup Duration Derivative	Primary Pain Outcomes (Response, Severity)	Overall Function/Disability (Including Pain Interference)	Serious Adverse Events and Withdrawals Due to Adverse Events
Vigil, 2017[b] High Preliminary historical cohort Mixed musculoskeletal pain	A: THC/CBD: Participation in New Mexico Medical Cannabis Program (37) B: Not participating in medical marijuana program and not using cannabis (29) 21 months Unknown THC concentration	NR	NR	NR
Ware, 2015 High Prospective cohort Chronic non-cancer pain	A: THC 12.5 +/- 1.5% herbal cannabis, median dose 2.5 g/day (215) B: Usual care (216) 13 months Whole plant non-extracted	NR	NR	SAE: 28/215 (13%) vs. 42/216 (19.4%), RR 0.67 (95% CI 0.43 to 1.04) WAE: 10/215 (4.65%) vs. NR (assumed 0), RR 21.10 95% CI 1.24 to 357.80)

Abbreviations: BPI = Brief Pain Inventory; CI = confidence interval; CBD = cannabidiol; IQR = interquartile range; MD = mean difference; NR = not reported; OR = odds ratio; SAE = serious adverse events; SD = standard deviation; SF−36= Short Form−36; THC = tetrahydrocannabinol; VAS = visual analog scale; WAE = withdrawal due to due adverse events.

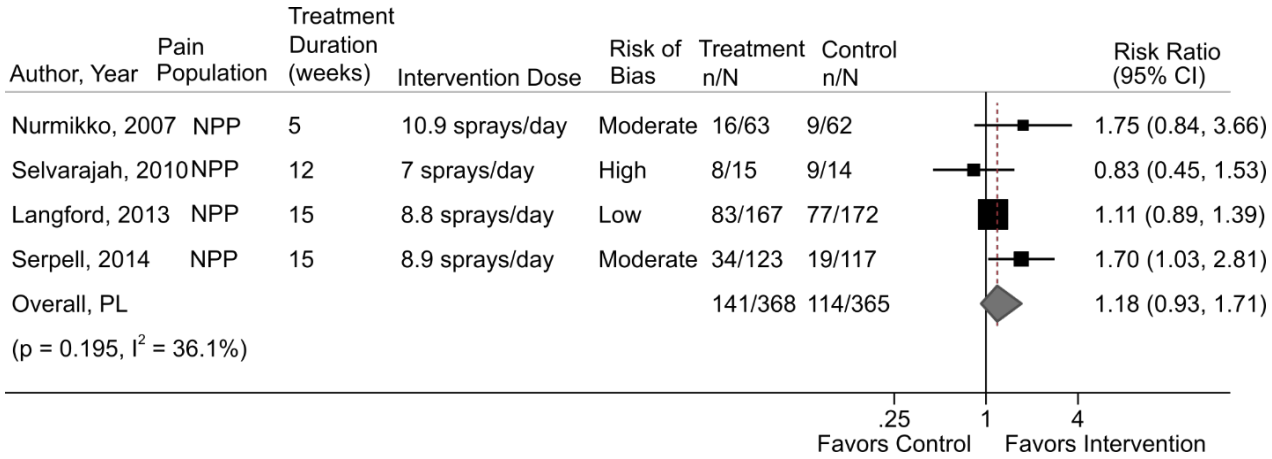
[a] Higher scores indicate better outcomes.

[b] Only included outcome reported was opioid-use.

Appendix D-2. Meta-Analyses

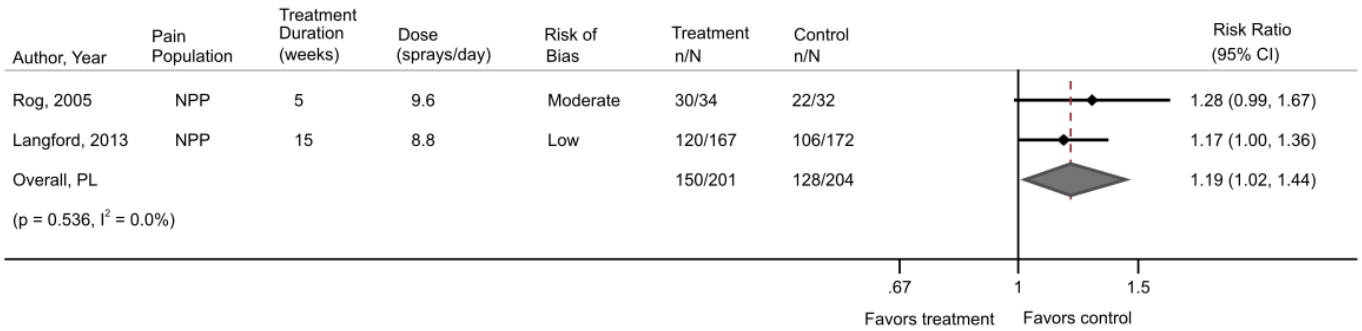
Comparable THC to CBD Ratio Studies

Figure D-1. Proportion of patients with pain response (≥30% improvement) with comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Nurmikko, 2007 NPP 5 10.9 sprays/day Moderate 16/63 9/62 1.75 (0.84, 3.66)
Selvarajah, 2010 NPP 12 7 sprays/day High 8/15 9/14 0.83 (0.45, 1.53)
Langford, 2013 NPP 15 8.8 sprays/day Low 83/167 77/172 1.11 (0.89, 1.39)
Serpell, 2014 NPP 15 8.9 sprays/day Moderate 34/123 19/117 1.70 (1.03, 2.81)
Overall, PL 141/368 114/365 1.18 (0.93, 1.71)
(p = 0.195, I² = 36.1%)
.25
1
4
Favors Control
Favors Intervention

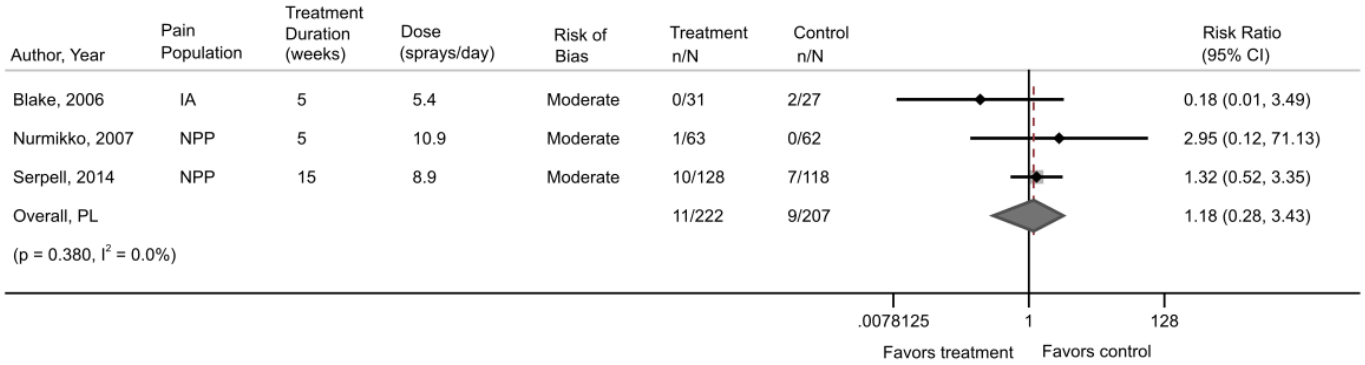
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood

Figure D-2. Adverse events for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)



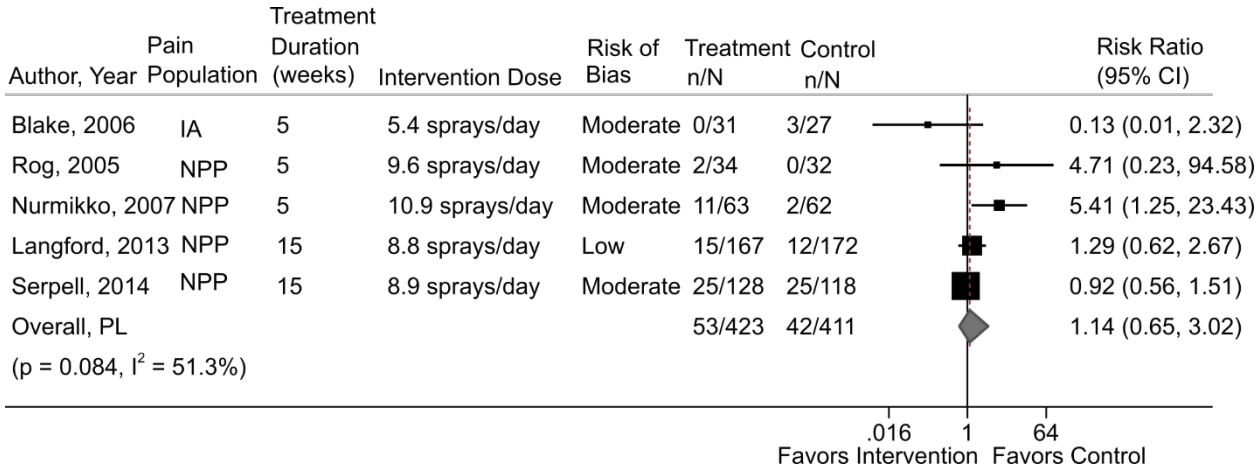
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood

Figure D-3. Serious adverse events for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Dose (sprays/day)
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Blake, 2006 IA 5 5.4 Moderate 0/31 2/27 0.18 (0.01, 3.49)
Nurmikko, 2007 NPP 5 10.9 Moderate 1/63 0/62 2.95 (0.12, 71.13)
Serpell, 2014 NPP 15 8.9 Moderate 10/128 7/118 1.32 (0.52, 3.35)
Overall, PL 11/222 9/207 1.18 (0.28, 3.43)
(p = 0.380, I² = 0.0%)
.0078125
1
128
Favors treatment
Favors control

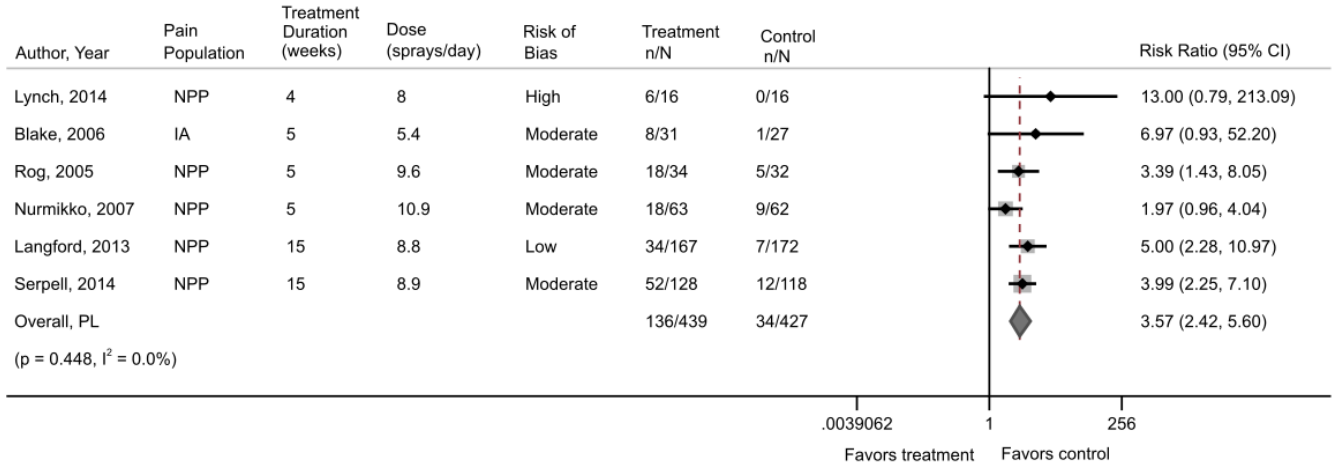
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

Figure D-4. Study withdrawal due to adverse events for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Blake, 2006 IA 5 5.4 sprays/day Moderate 0/31 3/27 0.13 (0.01, 2.32)
Rog, 2005 NPP 5 9.6 sprays/day Moderate 2/34 0/32 4.71 (0.23, 94.58)
Nurmikko, 2007 NPP 5 10.9 sprays/day Moderate 11/63 2/62 5.41 (1.25, 23.43)
Langford, 2013 NPP 15 8.8 sprays/day Low 15/167 12/172 1.29 (0.62, 2.67)
Serpell, 2014 NPP 15 8.9 sprays/day Moderate 25/128 25/118 0.92 (0.56, 1.51)
Overall, PL 53/423 42/411 1.14 (0.65, 3.02)
(p = 0.084, I² = 51.3%)
.016
1
64
Favors Intervention
Favors Control

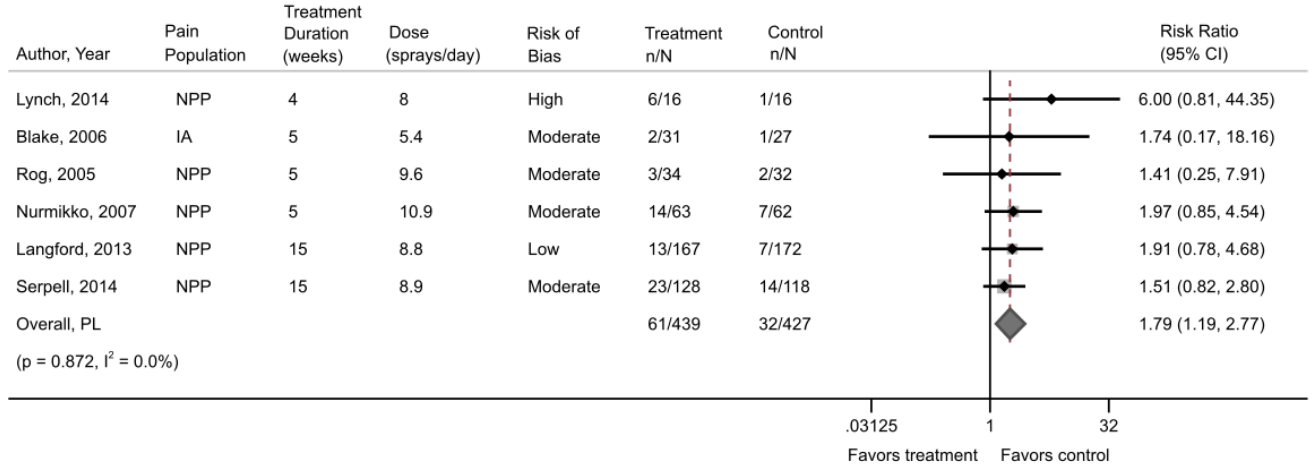
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

Figure D-5. Dizziness for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Dose (sprays/day)
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Lynch, 2014 NPP 4 8 High 6/16 0/16 13.00 (0.79, 213.09)
Blake, 2006 IA 5 5.4 Moderate 8/31 1/27 6.97 (0.93, 52.20)
Rog, 2005 NPP 5 9.6 Moderate 18/34 5/32 3.39 (1.43, 8.05)
Nurmikko, 2007 NPP 5 10.9 Moderate 18/63 9/62 1.97 (0.96, 4.04)
Langford, 2013 NPP 15 8.8 Low 34/167 7/172 5.00 (2.28, 10.97)
Serpell, 2014 NPP 15 8.9 Moderate 52/128 12/118 3.99 (2.25, 7.10)
Overall, PL 136/439 34/427 3.57 (2.42, 5.60)
(p = 0.448, I² = 0.0%)
.0039062
1
256
Favors treatment
Favors control

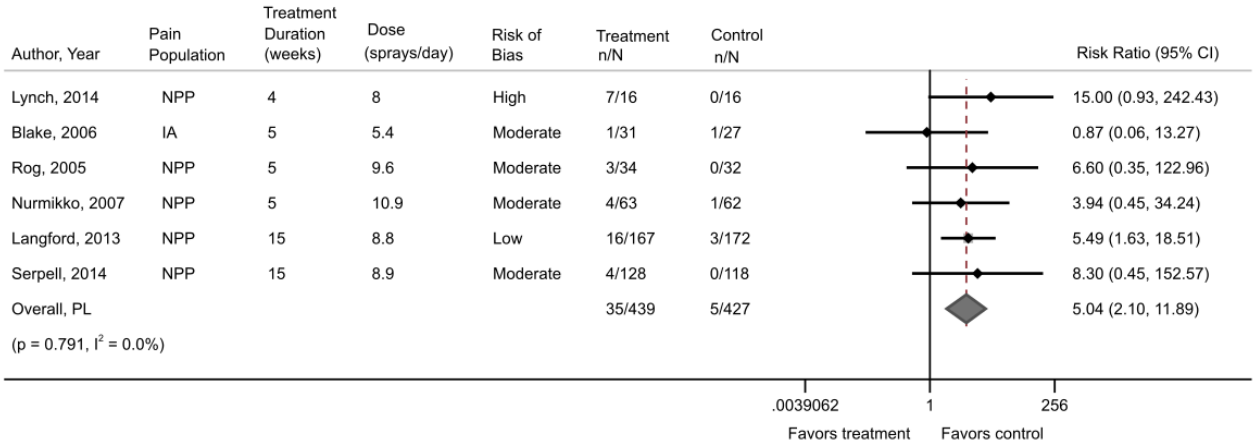
Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

Figure D-6. Nausea for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Dose (sprays/day)
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Lynch, 2014 NPP 4 8 High 6/16 1/16 6.00 (0.81, 44.35)
Blake, 2006 IA 5 5.4 Moderate 2/31 1/27 1.74 (0.17, 18.16)
Rog, 2005 NPP 5 9.6 Moderate 3/34 2/32 1.41 (0.25, 7.91)
Nurmikko, 2007 NPP 5 10.9 Moderate 14/63 7/62 1.97 (0.85, 4.54)
Langford, 2013 NPP 15 8.8 Low 13/167 7/172 1.91 (0.78, 4.68)
Serpell, 2014 NPP 15 8.9 Moderate 23/128 14/118 1.51 (0.82, 2.80)
Overall, PL 61/439 32/427 1.79 (1.19, 2.77)
(p = 0.872, I² = 0.0%)
.03125
1
32
Favors treatment
Favors control

Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

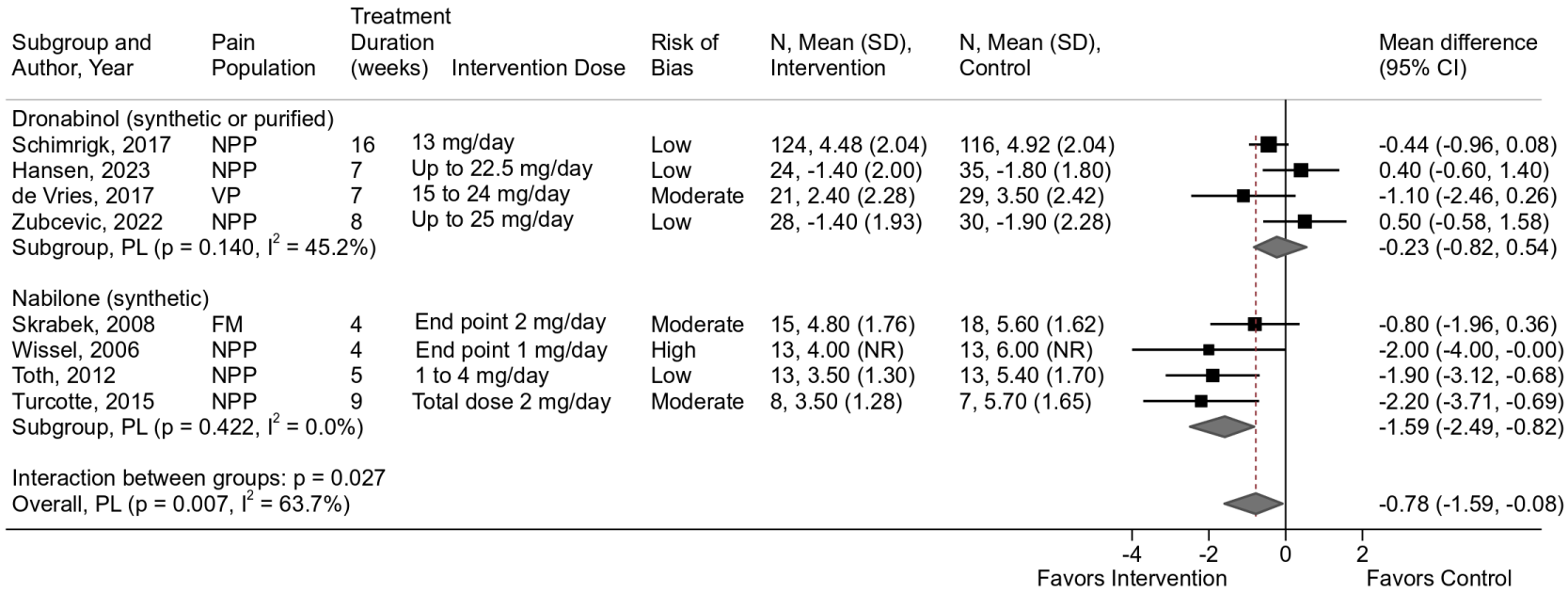
Figure D-7. Sedation for comparable THC to CBD ratio versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Dose (sprays/day)
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Lynch, 2014 NPP 4 8 High 7/16 0/16 15.00 (0.93, 242.43)
Blake, 2006 IA 5 5.4 Moderate 1/31 1/27 0.87 (0.06, 13.27)
Rog, 2005 NPP 5 9.6 Moderate 3/34 0/32 6.60 (0.35, 122.96)
Nurmikko, 2007 NPP 5 10.9 Moderate 4/63 1/62 3.94 (0.45, 34.24)
Langford, 2013 NPP 15 8.8 Low 16/167 3/172 5.49 (1.63, 18.51)
Serpell, 2014 NPP 15 8.9 Moderate 4/128 0/118 8.30 (0.45, 152.57)
Overall, PL 35/439 5/427 5.04 (2.10, 11.89)
(p = 0.791, I² = 0.0%)
.0039062
1
256
Favors treatment
Favors control

Abbreviations: CI = confidence interval; IA = inflammatory arthritis; NPP = neuropathic pain; PL = profile likelihood

High THC to CBD Ratio Studies

Figure D-8. Stratified results on pain severity of RCTs using dronabinol and nabilone (short-term, 1 to 6 months followup)


Subgroup and Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean difference (95% CI)
Dronabinol (synthetic or purified)
Schimrigk, 2017 NPP 16 13 mg/day Low 124, 4.48 (2.04) 116, 4.92 (2.04) -0.44 (-0.96, 0.08)
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 24, -1.40 (2.00) 35, -1.80 (1.80) 0.40 (-0.60, 1.40)
de Vries, 2017 VP 7 15 to 24 mg/day Moderate 21, 2.40 (2.28) 29, 3.50 (2.42) -1.10 (-2.46, 0.26)
Zubcevic, 2022 NPP 8 Up to 25 mg/day Low 28, -1.40 (1.93) 30, -1.90 (2.28) 0.50 (-0.58, 1.58)
Subgroup, PL (p = 0.140, I2 = 45.2%) -0.23 (-0.82, 0.54)
Nabilone (synthetic)
Skrabek, 2008 FM 4 End point 2 mg/day Moderate 15, 4.80 (1.76) 18, 5.60 (1.62) -0.80 (-1.96, 0.36)
Wissel, 2006 NPP 4 End point 1 mg/day High 13, 4.00 (NR) 13, 6.00 (NR) -2.00 (-4.00, -0.00)
Toth, 2012 NPP 5 1 to 4 mg/day Low 13, 3.50 (1.30) 13, 5.40 (1.70) -1.90 (-3.12, -0.68)
Turcotte, 2015 NPP 9 Total dose 2 mg/day Moderate 8, 3.50 (1.28) 7, 5.70 (1.65) -2.20 (-3.71, -0.69)
Subgroup, PL (p = 0.422, I2 = 0.0%) -1.59 (-2.49, -0.82)
Interaction between groups: p = 0.027
Overall, PL (p = 0.007, I2 = 63.7%) -0.78 (-1.59, -0.08)
-4
-2
0
2
Favors Intervention
Favors Control

Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; RCT = randomized controlled trial; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain

Table D-6. Interaction effect of randomized controlled trials assessing synthetic cannabinoids: nabilone versus dronabinol

Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.46	0.498	−2.92	0.027	−2.67 to −0.237

Table D-7. Meta-analysis results and sensitivity analysis using the Bartlett's correction

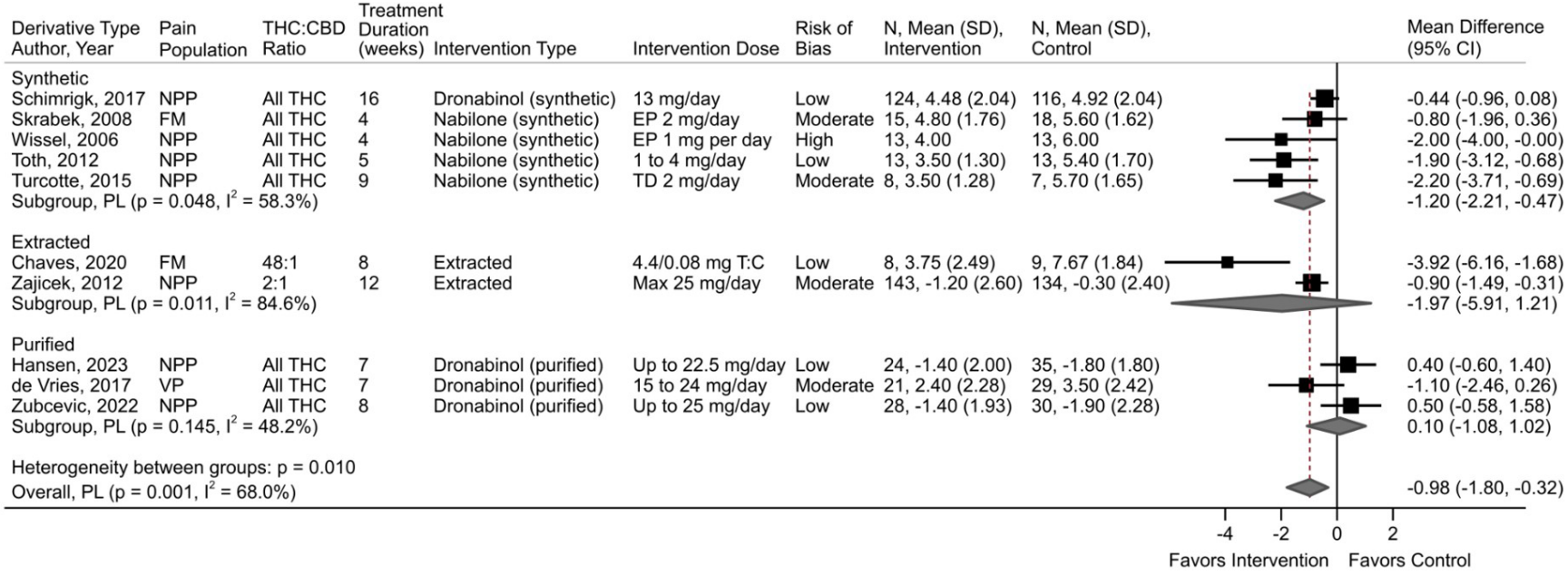
THC to CBD Ratio	Outcome	N; k Studies	Point Estimate	PL 95% CI	BC 95% CI	I-Squared
Comparable	Pain severity	N=702; k=7	MD −0.54	−0.95 to −0.19	−1.03 to −0.11	39%
Comparable	WAEs	N=834; k=5	RR 1.14	0.65 to 3.02	0.31 to 6.16	51%
Comparable	Dizziness	N=866; k=6	RR 3.57	2.42 to 5.60	2.15 to 6.62	0%
Comparable	Nausea	N=866; k=6	RR 1.79	1.19 to 2.77	1.06 to 3.32	0%
Comparable	Sedation	N=866; k=6	RR 5.04	2.10 to 11.89	1.41 to 17.29	0%
High (all)	Pain severity	N=801; k=10	MD −0.98	−1.80 to −0.32	−1.89 to −0.25	68%
High (synthetic or purified)	Pain severity	N=507; k=8	MD −0.78	−1.59 to −0.08	−1.71 to 0.01	64%
High (all)	WAEs	N=764; k=7	RR 2.32	1.41 to 4.43	1.13 to 5.83	0%
High (synthetic or purified)	WAEs	N=487; k=6	RR 1.92	1.10 to 4.80	0.69 to 9.12	0%
High (all)	Dizziness	N=709; k=5	RR 3.10	1.43 to 6.23	1.17 to 7.43	76%
High (all)	Sedation	N=458; k=5	RR 1.57	1.11 to 2.29	0.99 to 2.78	0%

Abbreviations: BC = Bartlett's correction; CBD = cannabidiol; CI = confidence interval; MD = mean difference; PL = profile likelihood; RR = relative risk; SAE = serious adverse event; THC = tetrahydrocannabinol; WAE = study withdrawals due to adverse event

Table D-8. Interaction effect of randomized controlled trials: synthetic or purified versus extracted interventions

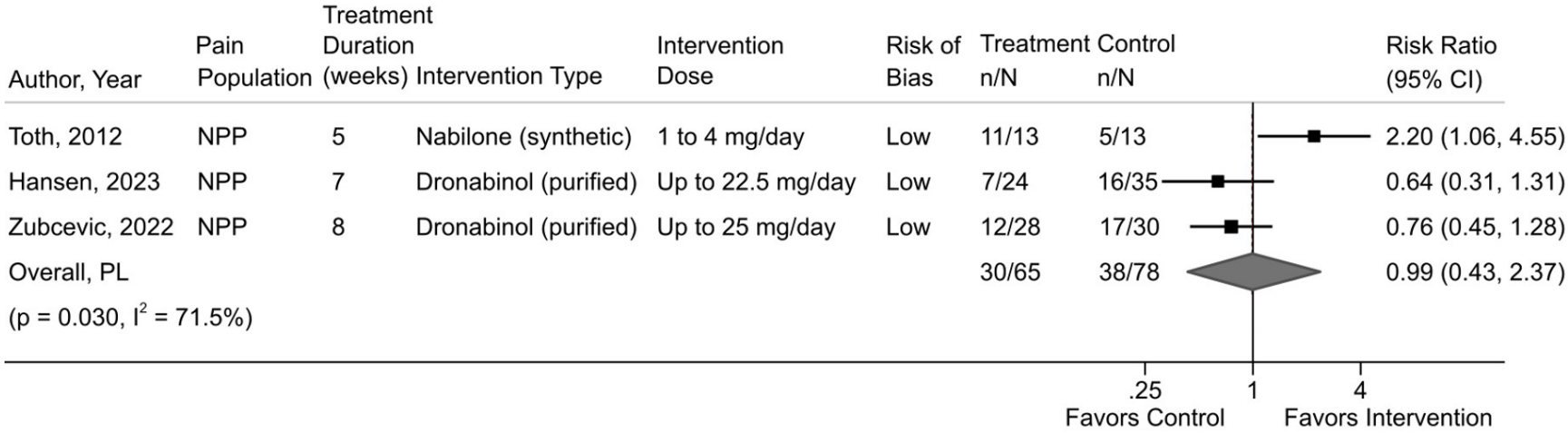
Group Difference	Coefficient	Standard Error	t-Test	p-Value	95% Confidence Interval
Result	−1.02	0.960	−1.07	0.318	−3.24 to 1.19

Figure D-9. Pain severity separated by synthetic and purified for high THC versus placebo (short-term, 1 to 6 months followup)


Derivative Type
Author, Year
Pain Population
THC:CBD Ratio
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean Difference (95% CI)
Synthetic
Schimrigk, 2017 NPP All THC 16 Dronabinol (synthetic) 13 mg/day Low 124, 4.48 (2.04) 116, 4.92 (2.04) -0.44 (-0.96, 0.08)
Skrabek, 2008 FM All THC 4 Nabilone (synthetic) EP 2 mg/day Moderate 15, 4.80 (1.76) 18, 5.60 (1.62) -0.80 (-1.96, 0.36)
Wissel, 2006 NPP All THC 4 Nabilone (synthetic) EP 1 mg per day High 13, 4.00 13, 6.00 -2.00 (-4.00, -0.00)
Toth, 2012 NPP All THC 5 Nabilone (synthetic) 1 to 4 mg/day Low 13, 3.50 (1.30) 13, 5.40 (1.70) -1.90 (-3.12, -0.68)
Turcotte, 2015 NPP All THC 9 Nabilone (synthetic) TD 2 mg/day Moderate 8, 3.50 (1.28) 7, 5.70 (1.65) -2.20 (-3.71, -0.69)
Subgroup, PL (p = 0.048, I² = 58.3%) -1.20 (-2.21, -0.47)
Extracted
Chaves, 2020 FM 48:1 8 Extracted 4.4/0.08 mg T:C Low 8, 3.75 (2.49) 9, 7.67 (1.84) -3.92 (-6.16, -1.68)
Zajicek, 2012 NPP 2:1 12 Extracted Max 25 mg/day Moderate 143, -1.20 (2.60) 134, -0.30 (2.40) -0.90 (-1.49, -0.31)
Subgroup, PL (p = 0.011, I² = 84.6%) -1.97 (-5.91, 1.21)
Purified
Hansen, 2023 NPP All THC 7 Dronabinol (purified) Up to 22.5 mg/day Low 24, -1.40 (2.00) 35, -1.80 (1.80) 0.40 (-0.60, 1.40)
de Vries, 2017 VP All THC 7 Dronabinol (purified) 15 to 24 mg/day Moderate 21, 2.40 (2.28) 29, 3.50 (2.42) -1.10 (-2.46, 0.26)
Zubcevic, 2022 NPP All THC 8 Dronabinol (purified) Up to 25 mg/day Low 28, -1.40 (1.93) 30, -1.90 (2.28) 0.50 (-0.58, 1.58)
Subgroup, PL (p = 0.145, I² = 48.2%) 0.10 (-1.08, 1.02)
Heterogeneity between groups: p = 0.010
Overall, PL (p = 0.001, I² = 68.0%) -0.98 (-1.80, -0.32)
-4
-2
0
2
Favors Intervention
Favors Control

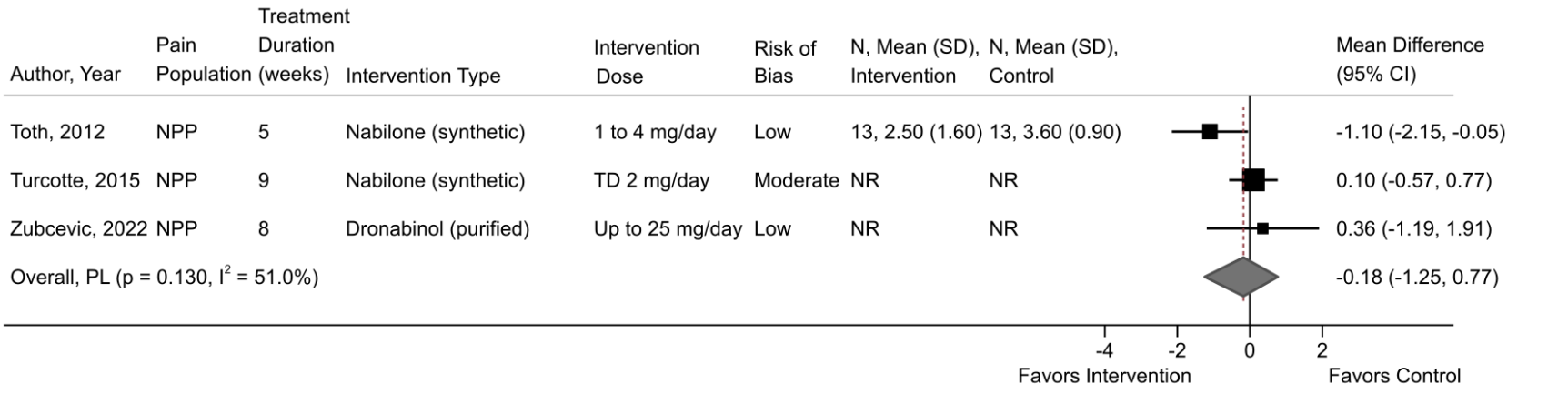
Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain.

Figure D-10. Proportion of patients with pain response (≥30% improvement) with high THC versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Toth, 2012 NPP 5 Nabilone (synthetic) 1 to 4 mg/day Low 11/13 5/13 2.20 (1.06, 4.55)
Hansen, 2023 NPP 7 Dronabinol (purified) Up to 22.5 mg/day Low 7/24 16/35 0.64 (0.31, 1.31)
Zubcevic, 2022 NPP 8 Dronabinol (purified) Up to 25 mg/day Low 12/28 17/30 0.76 (0.45, 1.28)
Overall, PL 30/65 38/78 0.99 (0.43, 2.37)
(p = 0.030, I² = 71.5%)
.25
1
4
Favors Control
Favors Intervention

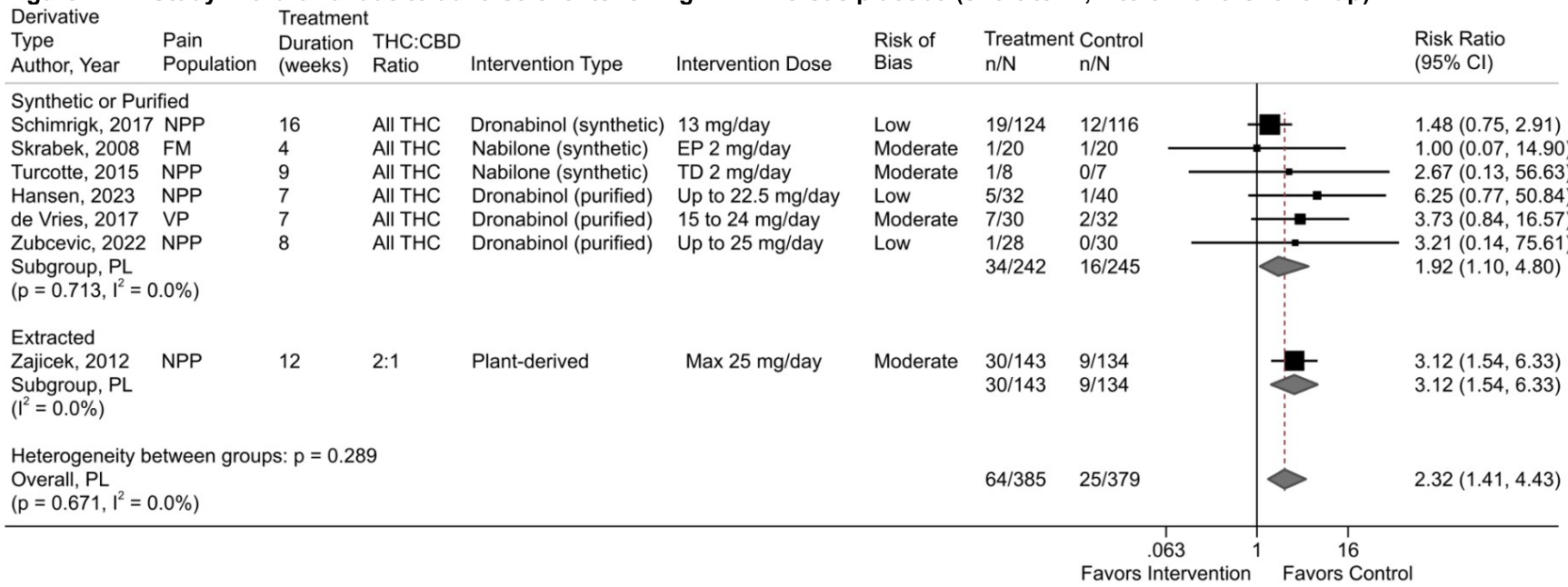
Abbreviations: CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

Figure D-11 Overall function for high THC versus placebo (short-term, 1 to 6 months followup)


Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean Difference (95% CI)
Toth, 2012 NPP 5 Nabilone (synthetic) 1 to 4 mg/day Low 13, 2.50 (1.60) 13, 3.60 (0.90) -1.10 (-2.15, -0.05)
Turcotte, 2015 NPP 9 Nabilone (synthetic) TD 2 mg/day Moderate NR NR 0.10 (-0.57, 0.77)
Zubcevic, 2022 NPP 8 Dronabinol (purified) Up to 25 mg/day Low NR NR 0.36 (-1.19, 1.91)
Overall, PL (p = 0.130, I² = 51.0%) -0.18 (-1.25, 0.77)
-4
-2
0
2
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; NR = not reported; SD = standard deviation; THC = tetrahydrocannabinol

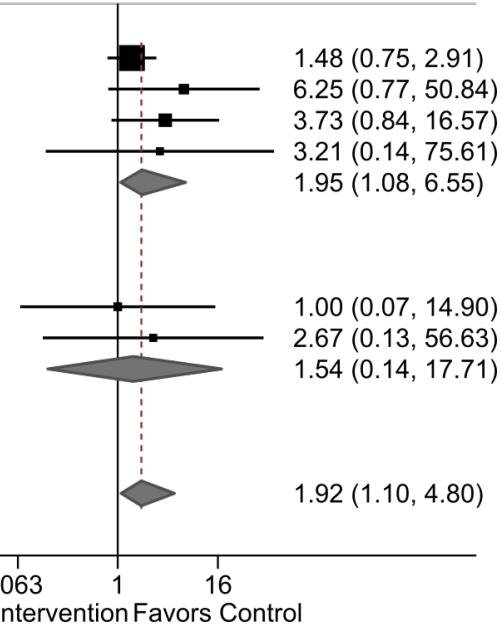
Figure D-12. Study withdrawal due to adverse events for high THC versus placebo (short-term, 1 to 6 months followup)


Derivative Type
Author, Year
Pain Population
Treatment Duration (weeks)
THC:CBD Ratio
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic or Purified
Schimrigk, 2017 NPP 16 All THC Dronabinol (synthetic) 13 mg/day Low 19/124 12/116 1.48 (0.75, 2.91)
Skrabek, 2008 FM 4 All THC Nabilone (synthetic) EP 2 mg/day Moderate 1/20 1/20 1.00 (0.07, 14.90)
Turcotte, 2015 NPP 9 All THC Nabilone (synthetic) TD 2 mg/day Moderate 1/8 0/7 2.67 (0.13, 56.63)
Hansen, 2023 NPP 7 All THC Dronabinol (purified) Up to 22.5 mg/day Low 5/32 1/40 6.25 (0.77, 50.84)
de Vries, 2017 VP 7 All THC Dronabinol (purified) 15 to 24 mg/day Moderate 7/30 2/32 3.73 (0.84, 16.57)
Zubcevic, 2022 NPP 8 All THC Dronabinol (purified) Up to 25 mg/day Low 1/28 0/30 3.21 (0.14, 75.61)
Subgroup, PL 34/242 16/245 1.92 (1.10, 4.80)
(p = 0.713, I² = 0.0%)
Extracted
Zajicek, 2012 NPP 12 2:1 Plant-derived Max 25 mg/day Moderate 30/143 9/134 3.12 (1.54, 6.33)
Subgroup, PL 30/143 9/134 3.12 (1.54, 6.33)
(I² = 0.0%)
Heterogeneity between groups: p = 0.289
Overall, PL 64/385 25/379 2.32 (1.41, 4.43)
(p = 0.671, I² = 0.0%)
.063
1
16
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain

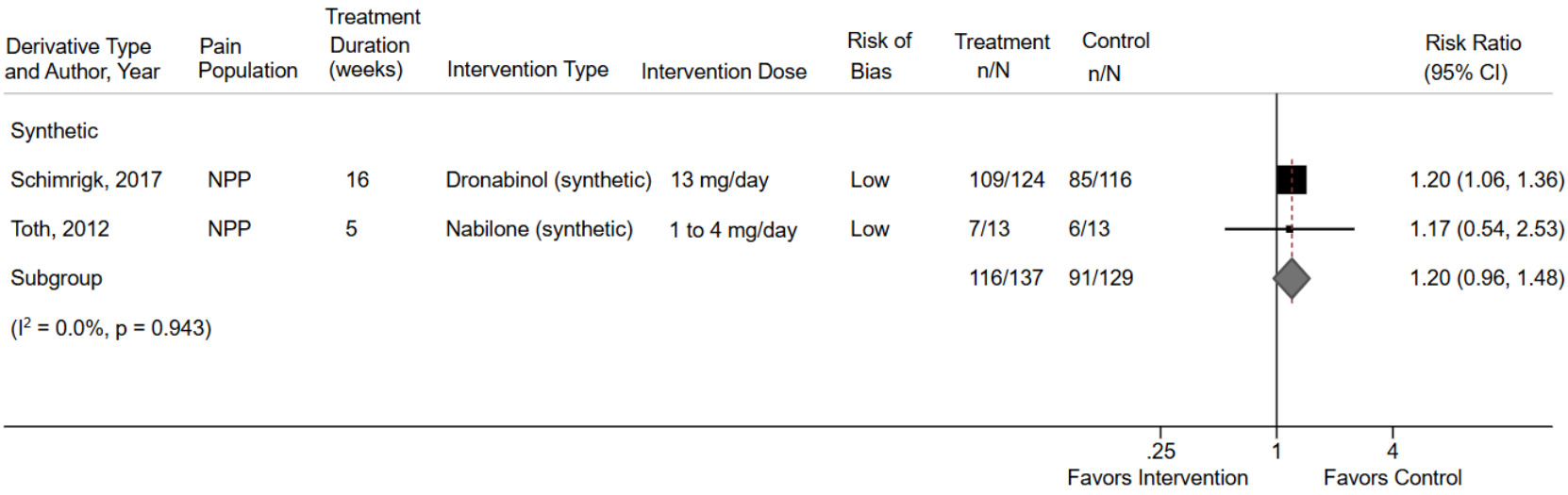
Figure D-13. Study withdrawal due to adverse events for dronabinol or nabilone versus placebo (short-term, 1 to 6 months followup)

Subgroup and Author, Year	Pain Population	Treatment Duration (weeks)	THC/CBD Ratio	Intervention Dose	Risk of Bias	Treatment n/N	Control n/N	Risk Ratio (95% CI)
Dronabinol (purified or synthetic)								
Schimrigk, 2017	NPP	16	All THC	13 mg/day	Low	19/124	12/116	1.48 (0.75, 2.91)
Hansen, 2023	NPP	7	All THC	Up to 22.5 mg/day	Low	5/32	1/40	6.25 (0.77, 50.84)
de Vries, 2017	VP	7	All THC	15 to 24 mg/day	Moderate	7/30	2/32	3.73 (0.84, 16.57)
Zubcevic, 2022	NPP	8	All THC	Up to 25 mg/day	Low	1/28	0/30	3.21 (0.14, 75.61)
Subgroup, PL ($p = 0.450$, $I^2 = 0.0\%$)						32/214	15/218	1.95 (1.08, 6.55)
Nabilone (synthetic)								
Skrabek, 2008	FM	4	All THC	EP 2 mg/day	Moderate	1/20	1/20	1.00 (0.07, 14.90)
Turcotte, 2015	NPP	9	All THC	TD 2 mg/day	Moderate	1/8	0/7	2.67 (0.13, 56.63)
Subgroup, PL ($p = 0.637$, $I^2 = 0.0\%$)						2/28	1/27	1.54 (0.14, 17.71)
Heterogeneity between groups: $p = 0.823$								
Overall, PL ($p = 0.713$, $I^2 = 0.0\%$)						34/242	16/245	1.92 (1.10, 4.80)



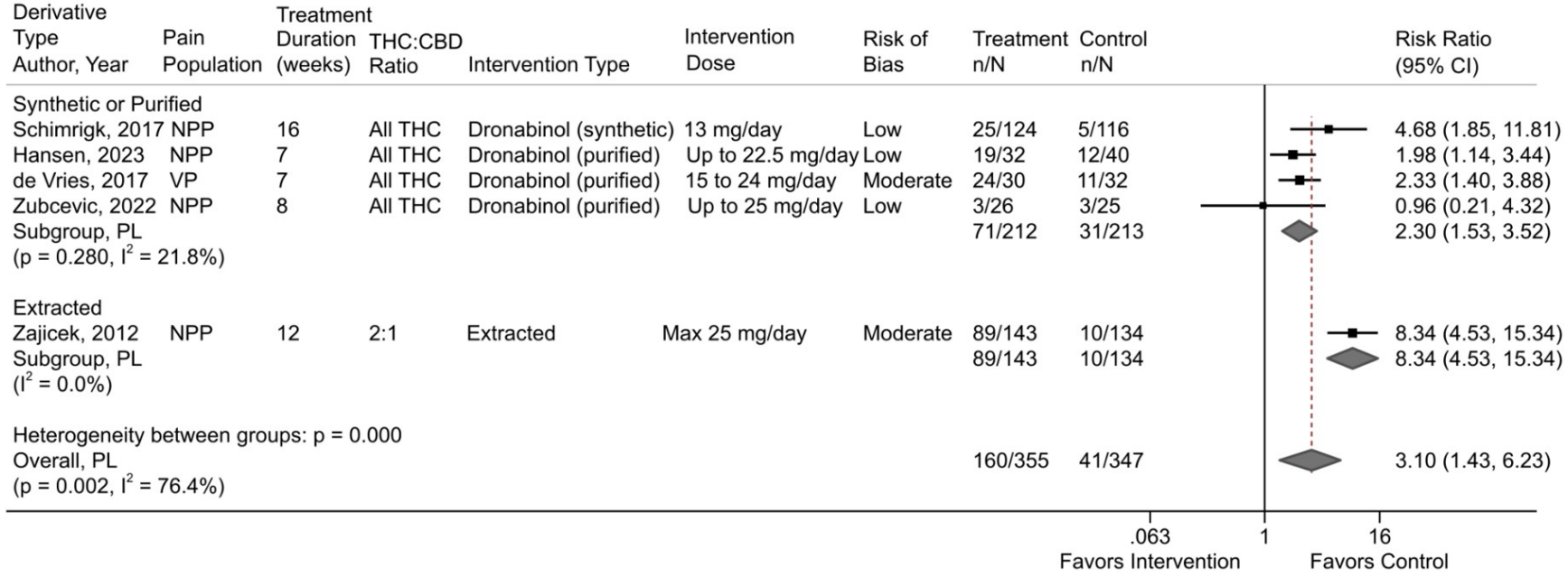
Abbreviations: CBD = cannabidiol; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; TD = total dose; THC = tetrahydrocannabinol; VP = visceral pain

Figure D-14. Any adverse event for high THC versus placebo (short-term, 1 to 6 months followup)



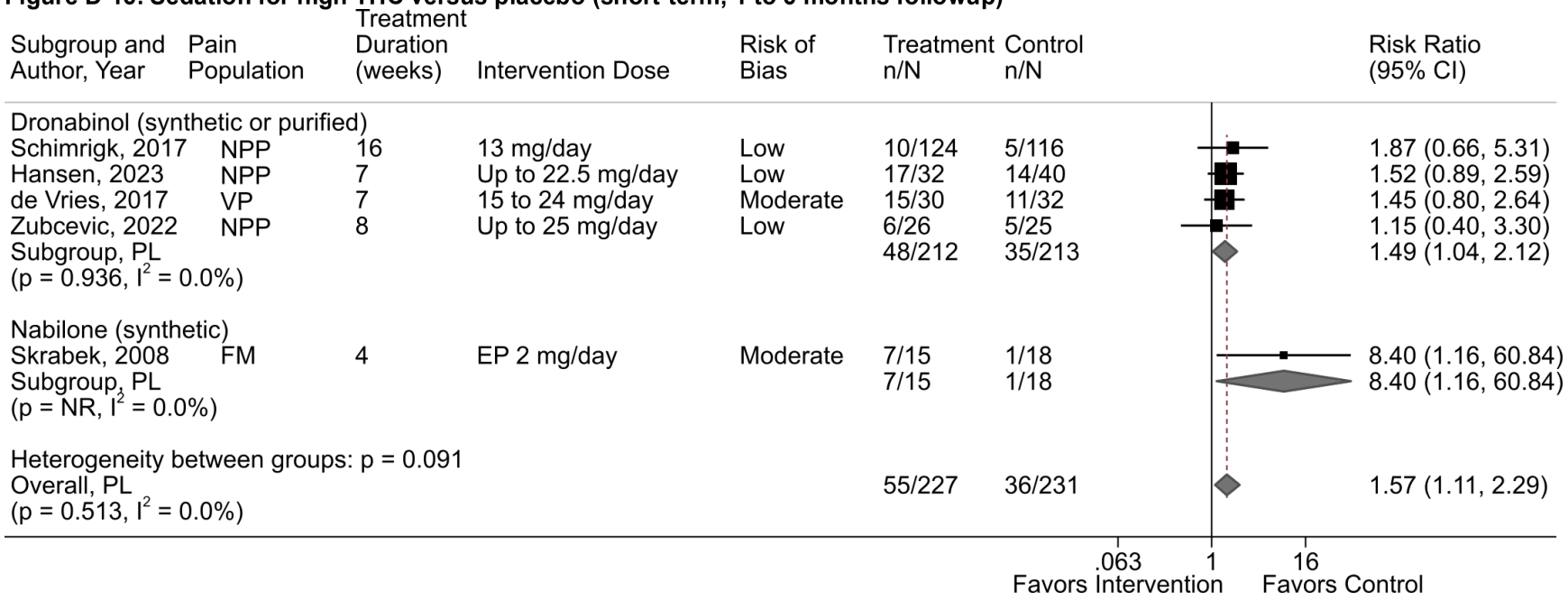
Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol

Figure D-15. Dizziness for high THC versus placebo (short-term, 1 to 6 months followup)


Derivative Type
Author, Year
Pain Population
Treatment Duration (weeks)
THC:CBD Ratio
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic or Purified
Schimrigk, 2017 NPP 16 All THC Dronabinol (synthetic) 13 mg/day Low 25/124 5/116 4.68 (1.85, 11.81)
Hansen, 2023 NPP 7 All THC Dronabinol (purified) Up to 22.5 mg/day Low 19/32 12/40 1.98 (1.14, 3.44)
de Vries, 2017 VP 7 All THC Dronabinol (purified) 15 to 24 mg/day Moderate 24/30 11/32 2.33 (1.40, 3.88)
Zubcevic, 2022 NPP 8 All THC Dronabinol (purified) Up to 25 mg/day Low 3/26 3/25 0.96 (0.21, 4.32)
Subgroup, PL 71/212 31/213 2.30 (1.53, 3.52)
(p = 0.280, I² = 21.8%)
Extracted
Zajicek, 2012 NPP 12 2:1 Extracted Max 25 mg/day Moderate 89/143 10/134 8.34 (4.53, 15.34)
Subgroup, PL 89/143 10/134 8.34 (4.53, 15.34)
(I² = 0.0%)
Heterogeneity between groups: p = 0.000
Overall, PL 160/355 41/347 3.10 (1.43, 6.23)
(p = 0.002, I² = 76.4%)
.063
1
16
Favors Intervention
Favors Control

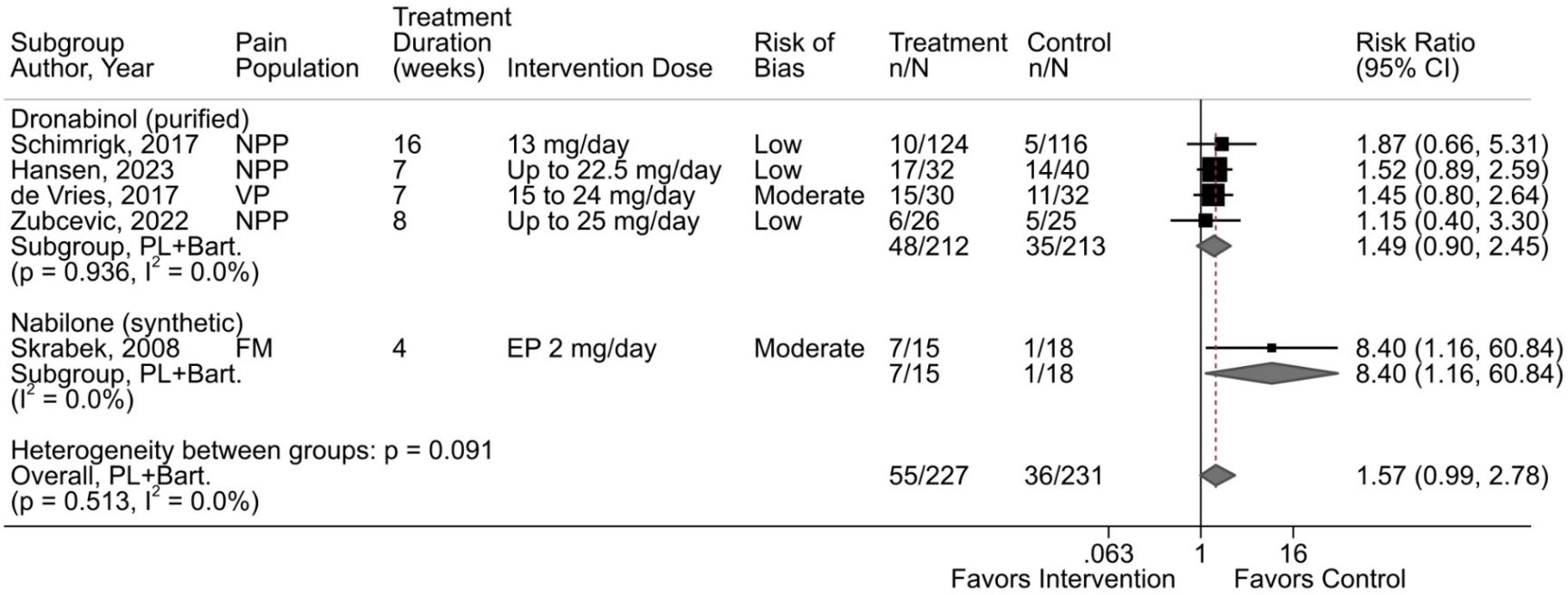
Abbreviations: CBD = cannabidiol; CI = confidence interval; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain

Figure D-16. Sedation for high THC versus placebo (short-term, 1 to 6 months followup)


Subgroup and Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Dronabinol (synthetic or purified)
Schimrigk, 2017 NPP 16 13 mg/day Low 10/124 5/116 1.87 (0.66, 5.31)
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 17/32 14/40 1.52 (0.89, 2.59)
de Vries, 2017 VP 7 15 to 24 mg/day Moderate 15/30 11/32 1.45 (0.80, 2.64)
Zubcevic, 2022 NPP 8 Up to 25 mg/day Low 6/26 5/25 1.15 (0.40, 3.30)
Subgroup, PL 48/212 35/213 1.49 (1.04, 2.12)
(p = 0.936, I² = 0.0%)
Nabilone (synthetic)
Skrabek, 2008 FM 4 EP 2 mg/day Moderate 7/15 1/18 8.40 (1.16, 60.84)
Subgroup, PL 7/15 1/18 8.40 (1.16, 60.84)
(p = NR, I² = 0.0%)
Heterogeneity between groups: p = 0.091
Overall, PL 55/227 36/231 1.57 (1.11, 2.29)
(p = 0.513, I² = 0.0%)
.063
1
16
Favors Intervention
Favors Control

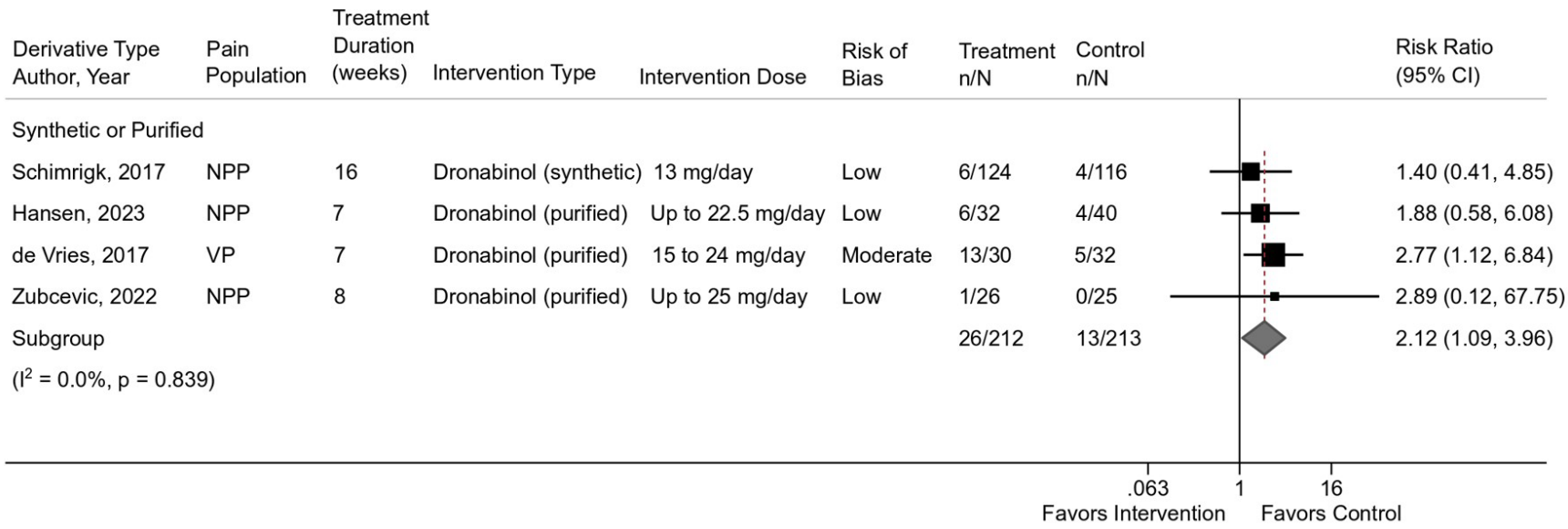
Abbreviations: CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL= profile likelihood; VP = visceral pain

Figure D-17. Sensitivity analysis of sedation for high THC versus placebo (short-term, 1 to 6 months followup)


Subgroup
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Dronabinol (purified)
Schimrigk, 2017 NPP 16 13 mg/day Low 10/124 5/116 1.87 (0.66, 5.31)
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 17/32 14/40 1.52 (0.89, 2.59)
de Vries, 2017 VP 7 15 to 24 mg/day Moderate 15/30 11/32 1.45 (0.80, 2.64)
Zubcevic, 2022 NPP 8 Up to 25 mg/day Low 6/26 5/25 1.15 (0.40, 3.30)
Subgroup, PL+Bart. 48/212 35/213 1.49 (0.90, 2.45)
(p = 0.936, I² = 0.0%)
Nabilone (synthetic)
Skrabek, 2008 FM 4 EP 2 mg/day Moderate 7/15 1/18 8.40 (1.16, 60.84)
Subgroup, PL+Bart. 7/15 1/18 8.40 (1.16, 60.84)
(I² = 0.0%)
Heterogeneity between groups: p = 0.091
Overall, PL+Bart. 55/227 36/231 1.57 (0.99, 2.78)
(p = 0.513, I² = 0.0%)
.063
1
16
Favors Intervention
Favors Control

Abbreviations: Bart = Bartlett's correction; CI = confidence interval; EP = end point; FM = fibromyalgia; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol; VP = visceral pain

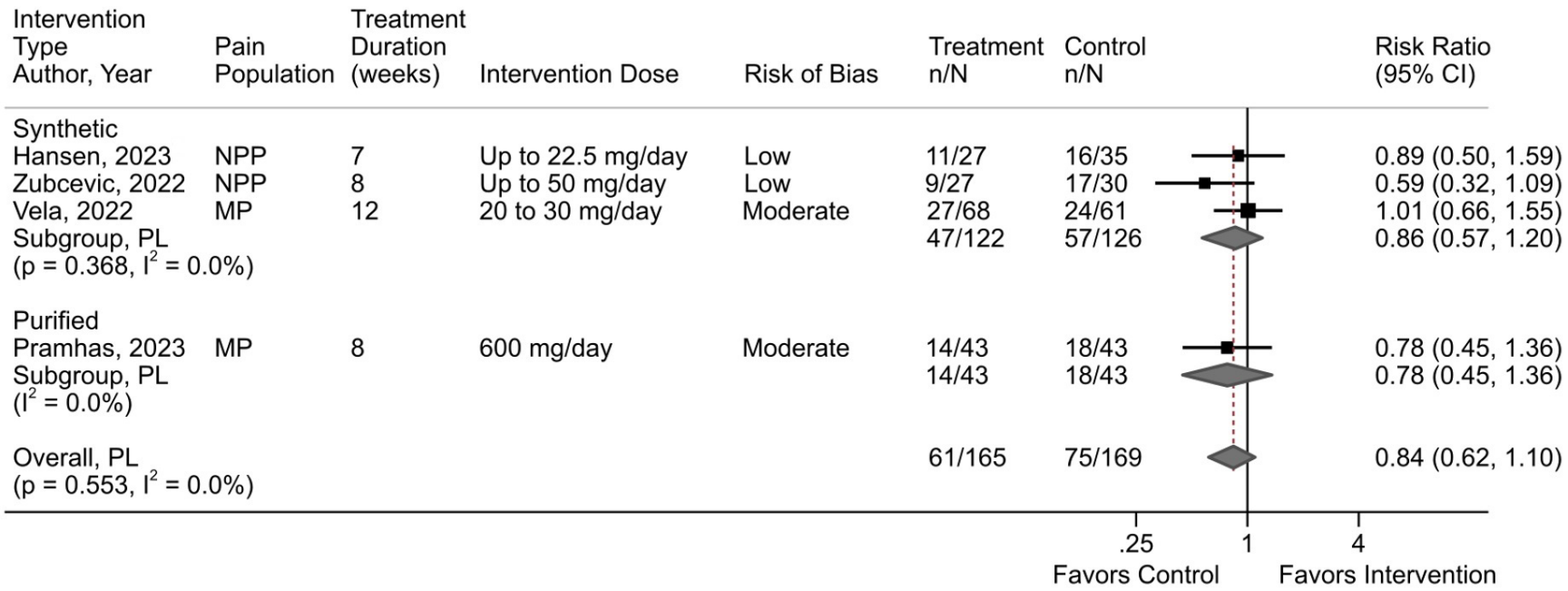
Figure D-18. Nausea for high THC versus placebo (short-term, 1 to 6 months followup)


Derivative Type
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic or Purified
Schimrigk, 2017 NPP 16 Dronabinol (synthetic) 13 mg/day Low 6/124 4/116 1.40 (0.41, 4.85)
Hansen, 2023 NPP 7 Dronabinol (purified) Up to 22.5 mg/day Low 6/32 4/40 1.88 (0.58, 6.08)
de Vries, 2017 VP 7 Dronabinol (purified) 15 to 24 mg/day Moderate 13/30 5/32 2.77 (1.12, 6.84)
Zubcevic, 2022 NPP 8 Dronabinol (purified) Up to 25 mg/day Low 1/26 0/25 2.89 (0.12, 67.75)
Subgroup 26/212 13/213 2.12 (1.09, 3.96)
(I^2 = 0.0%, p = 0.839)
.063
1
16
Favors Intervention
Favors Control

Abbreviations: CI = confidence interval; NPP = neuropathic pain; THC = tetrahydrocannabinol; VP = visceral pain

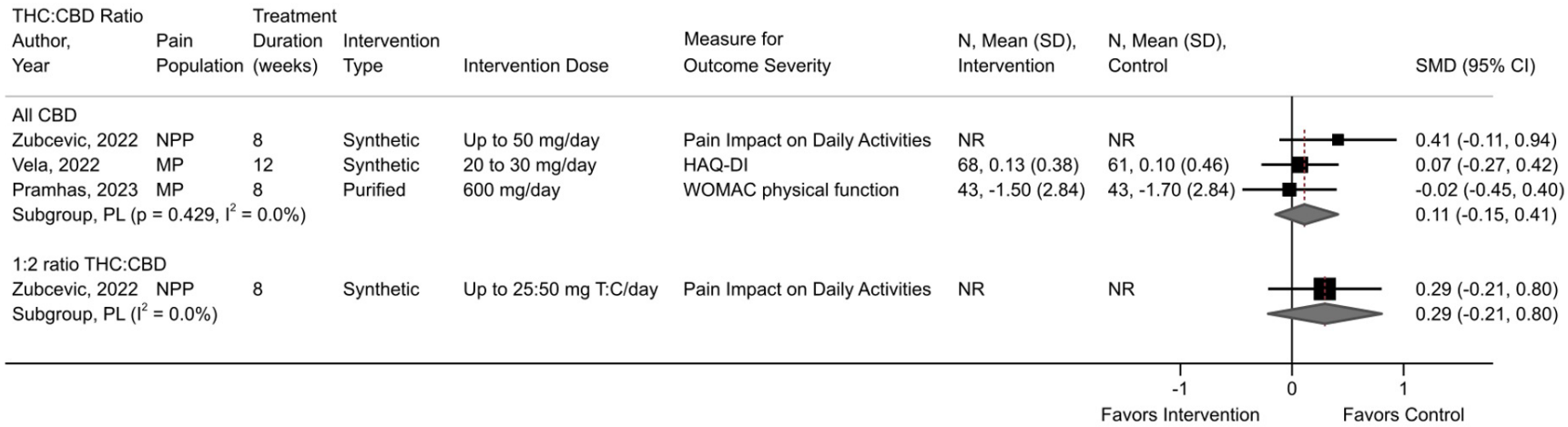
Low THC to CBD Ratio Studies

Figure D-19. Proportion of patients with pain response (≥30% improvement) for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)


Intervention Type
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 11/27 16/35 0.89 (0.50, 1.59)
Zubcevic, 2022 NPP 8 Up to 50 mg/day Low 9/27 17/30 0.59 (0.32, 1.09)
Vela, 2022 MP 12 20 to 30 mg/day Moderate 27/68 24/61 1.01 (0.66, 1.55)
Subgroup, PL 47/122 57/126 0.86 (0.57, 1.20)
(p = 0.368, I² = 0.0%)
Purified
Pramhas, 2023 MP 8 600 mg/day Moderate 14/43 18/43 0.78 (0.45, 1.36)
Subgroup, PL 14/43 18/43 0.78 (0.45, 1.36)
(I² = 0.0%)
Overall, PL 61/165 75/169 0.84 (0.62, 1.10)
(p = 0.553, I² = 0.0%)
.25
1
4
Favors Control
Favors Intervention

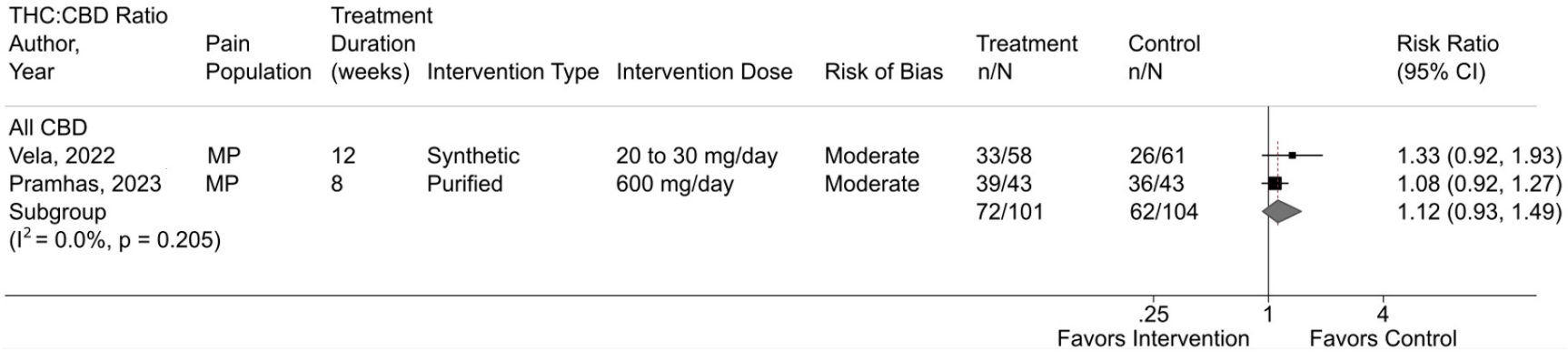
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

Figure D-20. Overall function for low THC versus placebo (short-term, 1 to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Measure for Outcome Severity
N, Mean (SD), Intervention
N, Mean (SD), Control
SMD (95% CI)
All CBD
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Pain Impact on Daily Activities NR NR 0.41 (-0.11, 0.94)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day HAQ-DI 68, 0.13 (0.38) 61, 0.10 (0.46) 0.07 (-0.27, 0.42)
Pramhas, 2023 MP 8 Purified 600 mg/day WOMAC physical function 43, -1.50 (2.84) 43, -1.70 (2.84) -0.02 (-0.45, 0.40)
Subgroup, PL (p = 0.429, I² = 0.0%) 0.11 (-0.15, 0.41)
1:2 ratio THC:CBD
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Pain Impact on Daily Activities NR NR 0.29 (-0.21, 0.80)
Subgroup, PL (I² = 0.0%) 0.29 (-0.21, 0.80)
-1
0
1
Favors Intervention
Favors Control

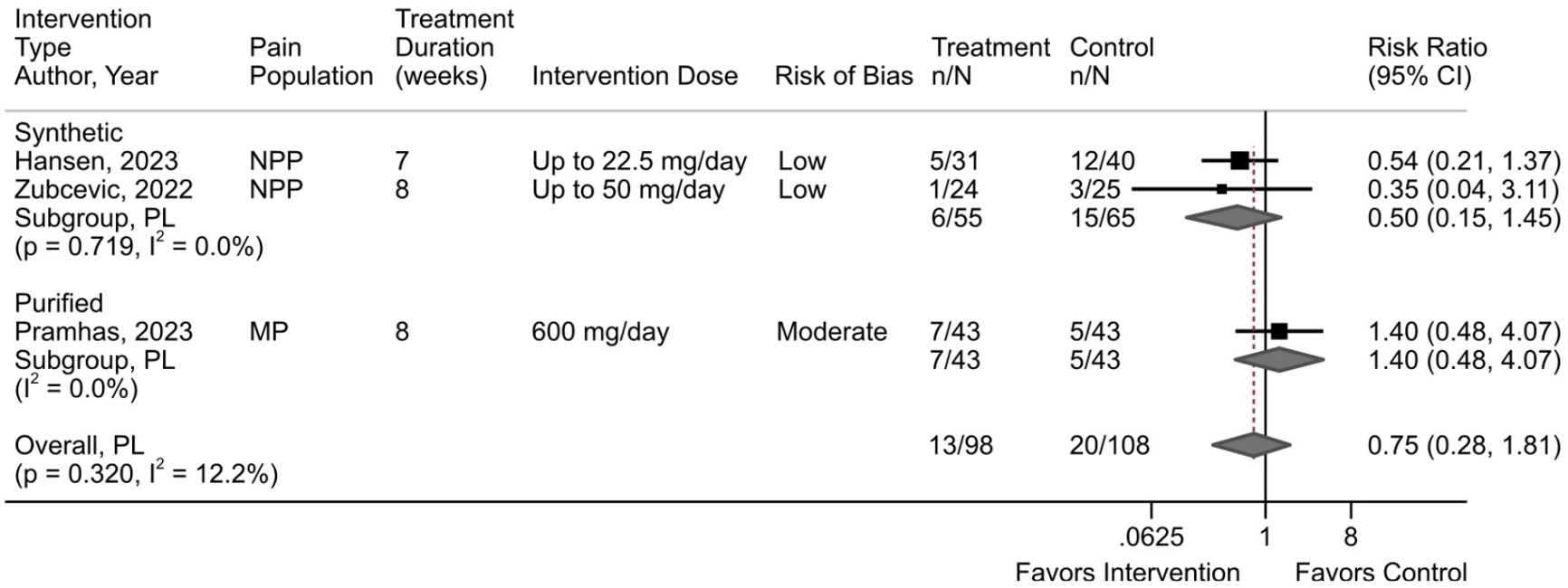
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol

Figure D-21. Any adverse event for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)



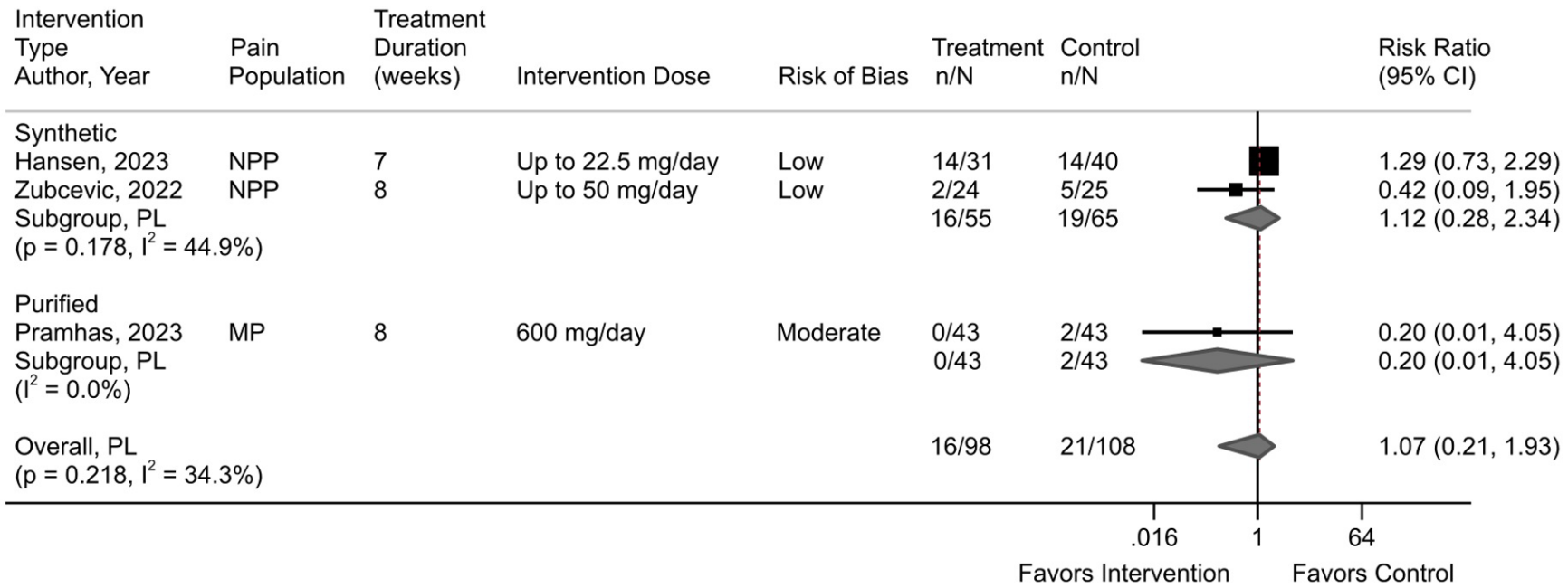
Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; THC = tetrahydrocannabinol

Figure D-22. Dizziness for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)


Intervention Type
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 5/31 12/40 0.54 (0.21, 1.37)
Zubcevic, 2022 NPP 8 Up to 50 mg/day Low 1/24 3/25 0.35 (0.04, 3.11)
Subgroup, PL 6/55 15/65 0.50 (0.15, 1.45)
(p = 0.719, I2 = 0.0%)
Purified
Pramhas, 2023 MP 8 600 mg/day Moderate 7/43 5/43 1.40 (0.48, 4.07)
Subgroup, PL 7/43 5/43 1.40 (0.48, 4.07)
(I2 = 0.0%)
Overall, PL 13/98 20/108 0.75 (0.28, 1.81)
(p = 0.320, I2 = 12.2%)
.0625
1
8
Favors Intervention
Favors Control

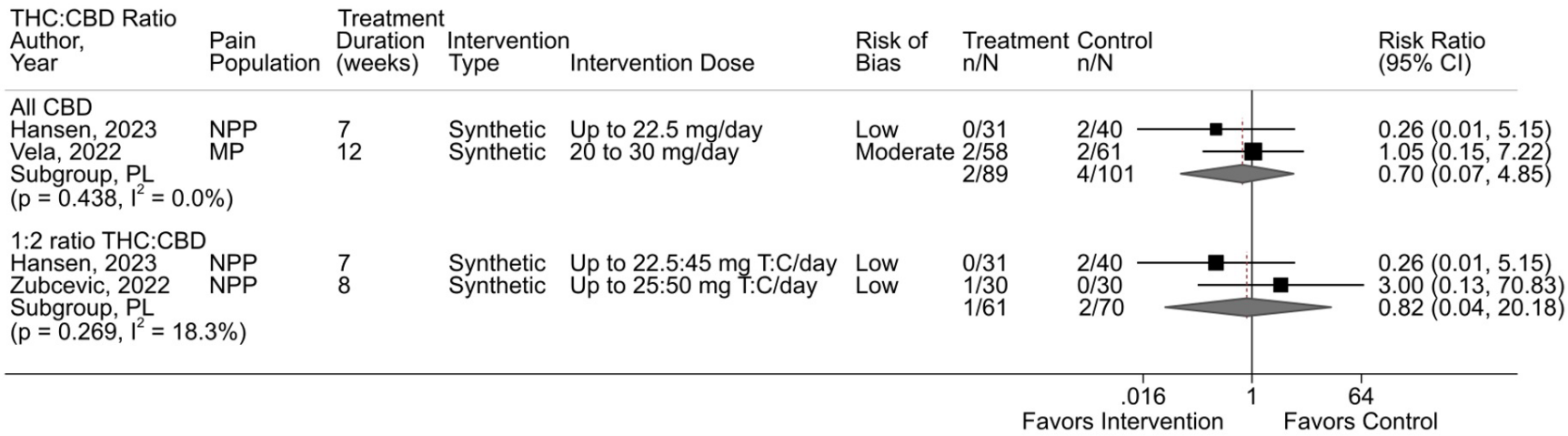
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

Figure D-23. Sedation for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)


Intervention Type Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 14/31 14/40 1.29 (0.73, 2.29)
Zubcevic, 2022 NPP 8 Up to 50 mg/day Low 2/24 5/25 0.42 (0.09, 1.95)
Subgroup, PL (p = 0.178, I2 = 44.9%) 16/55 19/65 1.12 (0.28, 2.34)
Purified
Pramhas, 2023 MP 8 600 mg/day Moderate 0/43 2/43 0.20 (0.01, 4.05)
Subgroup, PL (I2 = 0.0%) 0/43 2/43 0.20 (0.01, 4.05)
Overall, PL (p = 0.218, I2 = 34.3%) 16/98 21/108 1.07 (0.21, 1.93)
.016
1
64
Favors Intervention
Favors Control

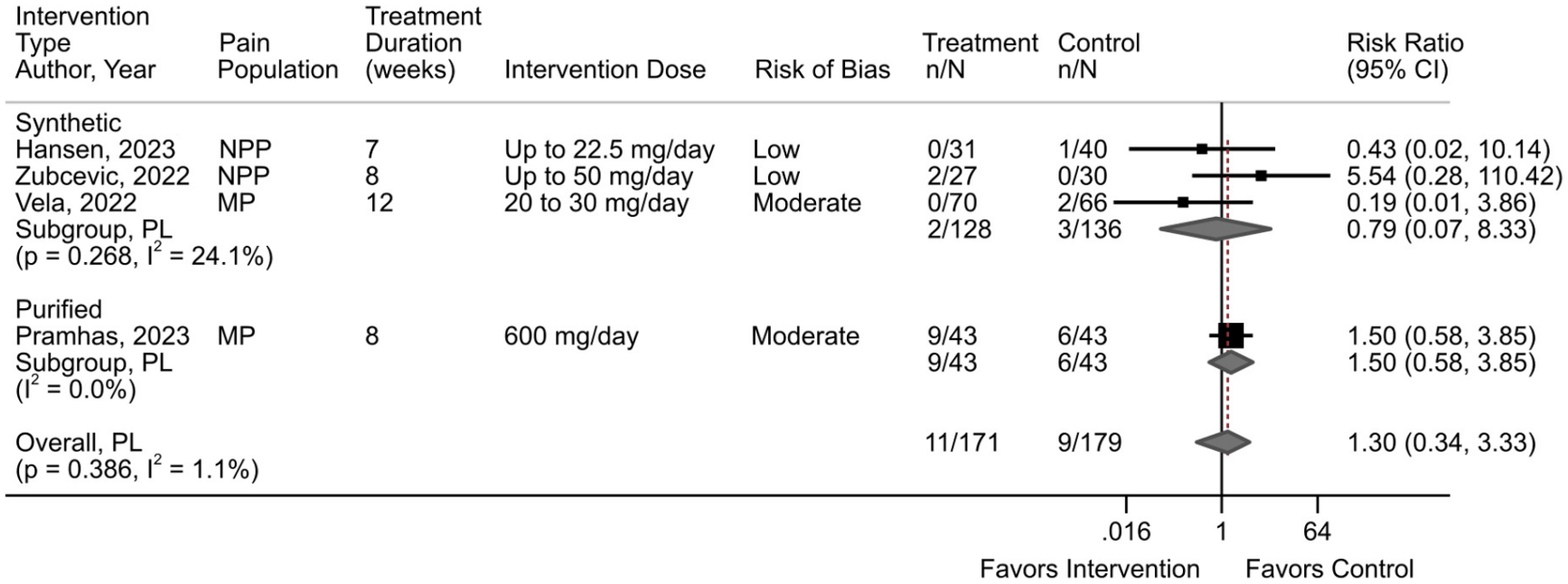
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

Figure D-24. Serious adverse events for low THC versus placebo (short-term, 1 to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 0/31 2/40 0.26 (0.01, 5.15)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day Moderate 2/58 2/61 1.05 (0.15, 7.22)
Subgroup, PL 2/89 4/101 0.70 (0.07, 4.85)
(p = 0.438, I² = 0.0%)
1:2 ratio THC:CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5:45 mg T:C/day Low 0/31 2/40 0.26 (0.01, 5.15)
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Low 1/30 0/30 3.00 (0.13, 70.83)
Subgroup, PL 1/61 2/70 0.82 (0.04, 20.18)
(p = 0.269, I² = 18.3%)
.016
1
64
Favors Intervention
Favors Control

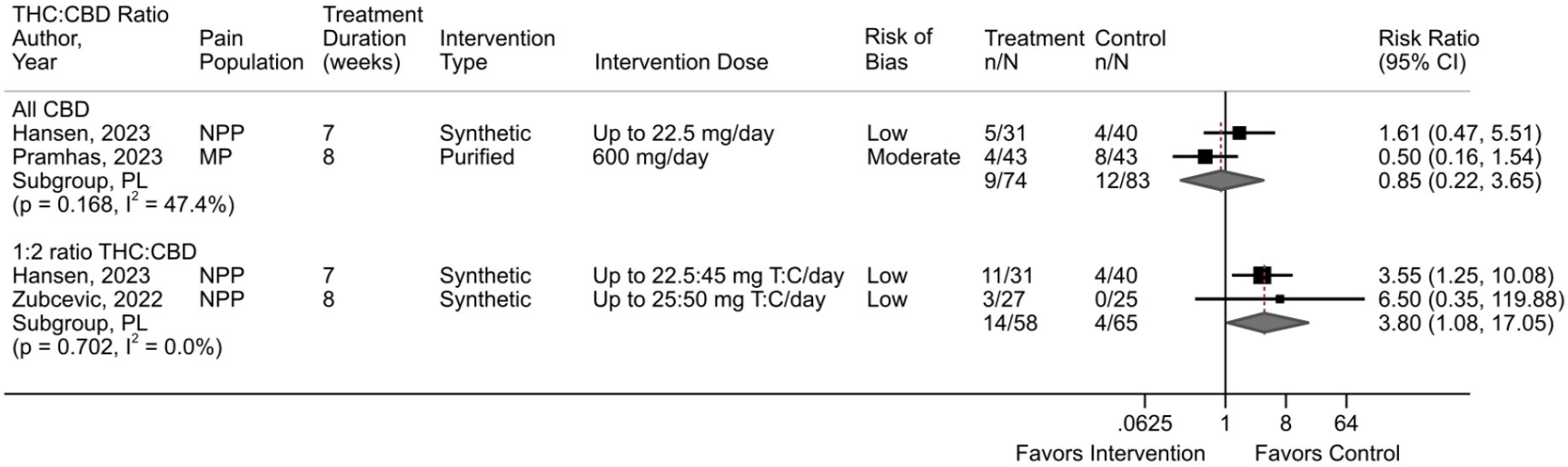
Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

Figure D-25. Study withdrawal due to adverse events for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)


Intervention Type
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
Synthetic
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 0/31 1/40 0.43 (0.02, 10.14)
Zubcevic, 2022 NPP 8 Up to 50 mg/day Low 2/27 0/30 5.54 (0.28, 110.42)
Vela, 2022 MP 12 20 to 30 mg/day Moderate 0/70 2/66 0.19 (0.01, 3.86)
Subgroup, PL 2/128 3/136 0.79 (0.07, 8.33)
(p = 0.268, I² = 24.1%)
Purified
Pramhas, 2023 MP 8 600 mg/day Moderate 9/43 6/43 1.50 (0.58, 3.85)
Subgroup, PL 9/43 6/43 1.50 (0.58, 3.85)
(I² = 0.0%)
Overall, PL 11/171 9/179 1.30 (0.34, 3.33)
(p = 0.386, I² = 1.1%)
.016
1
64
Favors Intervention
Favors Control

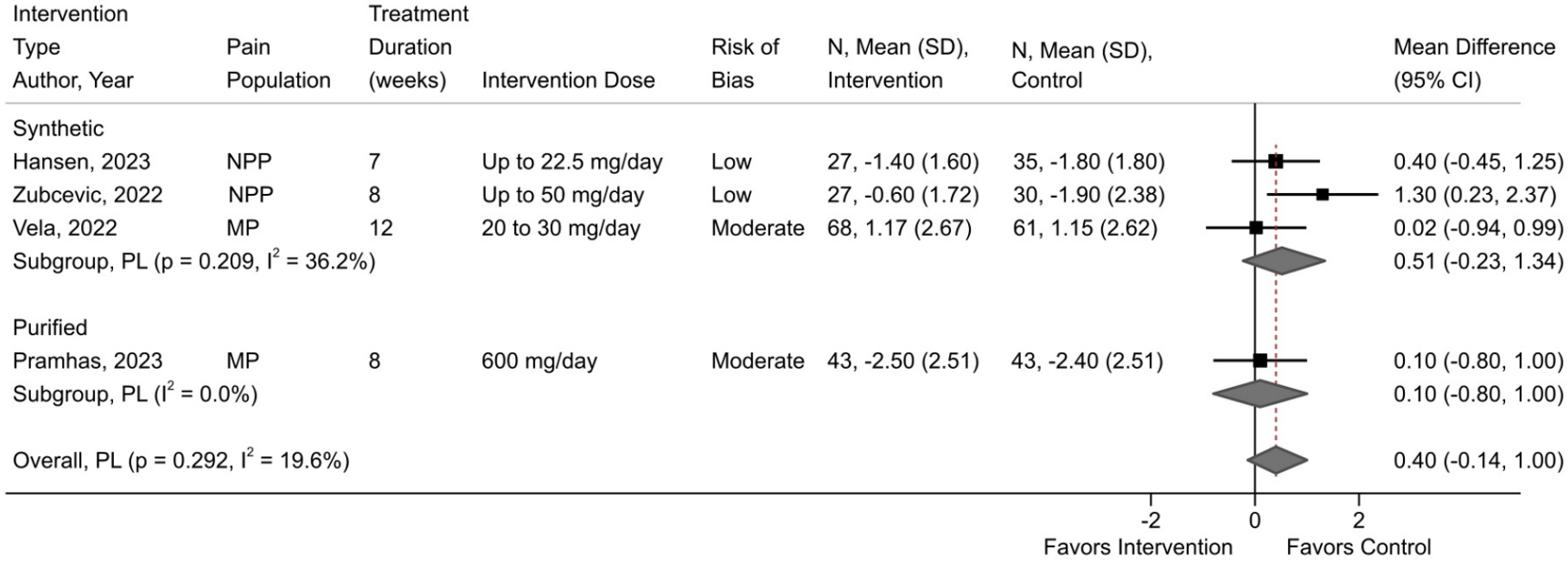
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; THC = tetrahydrocannabinol

Figure D-26. Nausea for low THC versus placebo (short-term, 1 to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 5/31 4/40 1.61 (0.47, 5.51)
Pramhas, 2023 MP 8 Purified 600 mg/day Moderate 4/43 8/43 0.50 (0.16, 1.54)
Subgroup, PL 9/74 12/83 0.85 (0.22, 3.65)
(p = 0.168, I² = 47.4%)
1:2 ratio THC:CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5:45 mg T:C/day Low 11/31 4/40 3.55 (1.25, 10.08)
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Low 3/27 0/25 6.50 (0.35, 119.88)
Subgroup, PL 14/58 4/65 3.80 (1.08, 17.05)
(p = 0.702, I² = 0.0%)
.0625
1
8
64
Favors Intervention
Favors Control

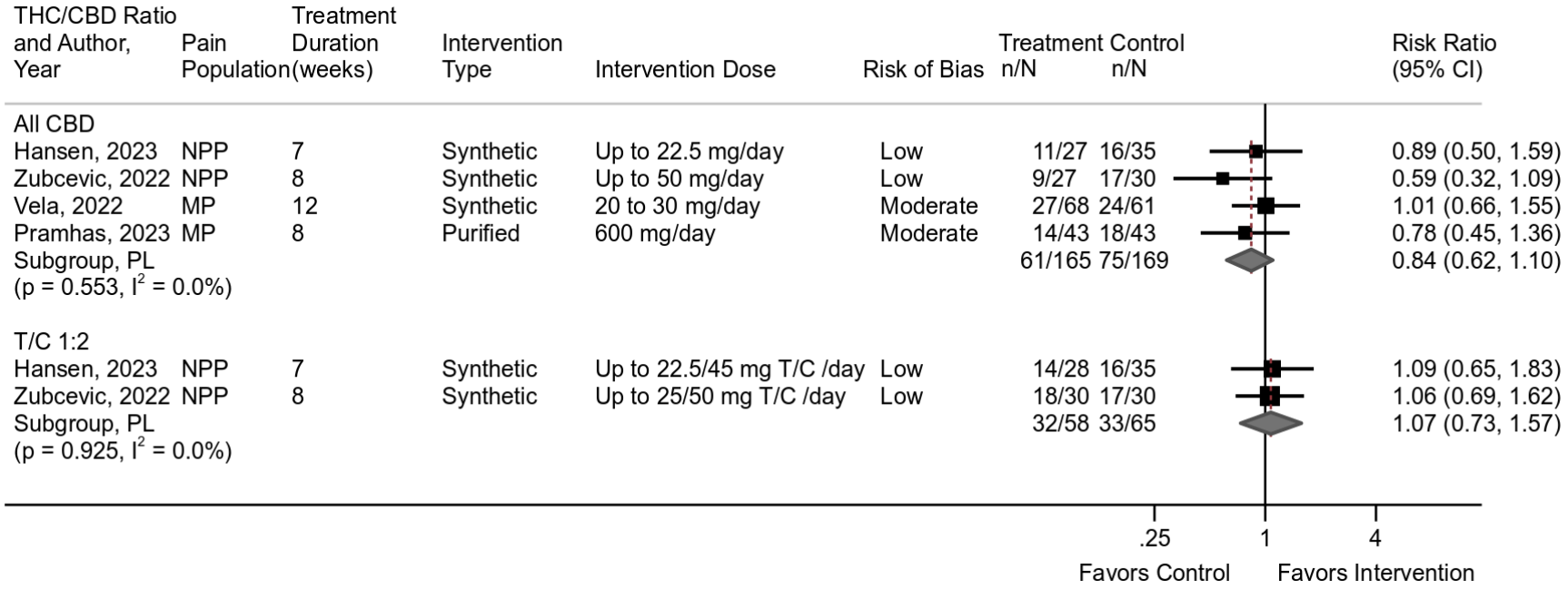
Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

Figure D-27. Pain intensity for low THC (CBD alone) versus placebo (short-term, 1 to 6 months followup)


Intervention Type
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Dose
Risk of Bias
N, Mean (SD), Intervention
N, Mean (SD), Control
Mean Difference (95% CI)
Synthetic
Hansen, 2023 NPP 7 Up to 22.5 mg/day Low 27, -1.40 (1.60) 35, -1.80 (1.80) 0.40 (-0.45, 1.25)
Zubcevic, 2022 NPP 8 Up to 50 mg/day Low 27, -0.60 (1.72) 30, -1.90 (2.38) 1.30 (0.23, 2.37)
Vela, 2022 MP 12 20 to 30 mg/day Moderate 68, 1.17 (2.67) 61, 1.15 (2.62) 0.02 (-0.94, 0.99)
Subgroup, PL (p = 0.209, I² = 36.2%) 0.51 (-0.23, 1.34)
Purified
Pramhas, 2023 MP 8 600 mg/day Moderate 43, -2.50 (2.51) 43, -2.40 (2.51) 0.10 (-0.80, 1.00)
Subgroup, PL (I² = 0.0%) 0.10 (-0.80, 1.00)
Overall, PL (p = 0.292, I² = 19.6%) 0.40 (-0.14, 1.00)
-2
0
2
Favors Intervention
Favors Control

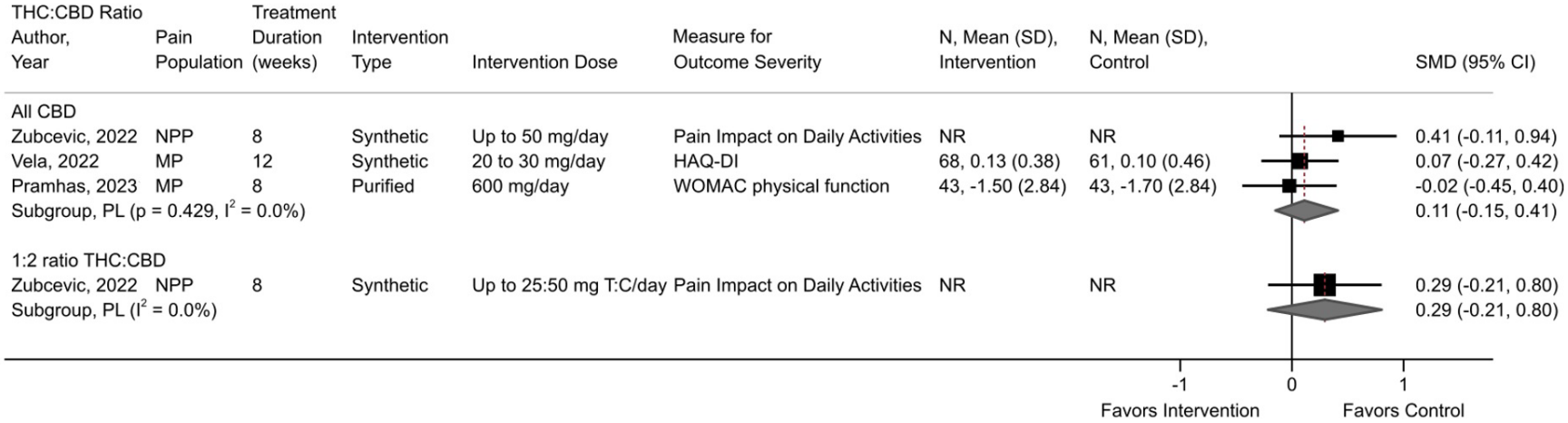
Abbreviations: CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; SD = standard deviation; THC = tetrahydrocannabinol

Figure D-28. Proportion of patients with pain response (≥30% improvement) separated by intervention type for low THC versus placebo (short-term, 1 to 6 months followup)


THC/CBD Ratio and Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 11/27 16/35 0.89 (0.50, 1.59)
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Low 9/27 17/30 0.59 (0.32, 1.09)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day Moderate 27/68 24/61 1.01 (0.66, 1.55)
Pramhas, 2023 MP 8 Purified 600 mg/day Moderate 14/43 18/43 0.78 (0.45, 1.36)
Subgroup, PL 61/165 75/169 0.84 (0.62, 1.10)
(p = 0.553, I² = 0.0%)
T/C 1:2
Hansen, 2023 NPP 7 Synthetic Up to 22.5/45 mg T/C /day Low 14/28 16/35 1.09 (0.65, 1.83)
Zubcevic, 2022 NPP 8 Synthetic Up to 25/50 mg T/C /day Low 18/30 17/30 1.06 (0.69, 1.62)
Subgroup, PL 32/58 33/65 1.07 (0.73, 1.57)
(p = 0.925, I² = 0.0%)
.25
1
4
Favors Control
Favors Intervention

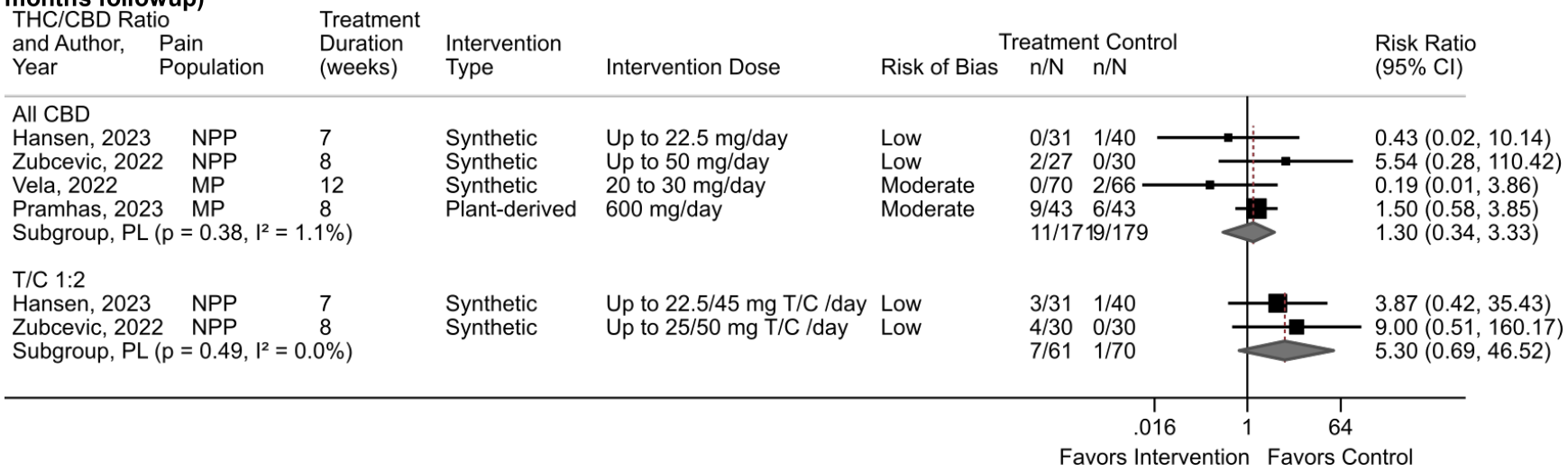
Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; TD = total dose; THC = tetrahydrocannabinol

Figure D-29. Overall function separated by intervention type for low THC versus placebo (short-term, 1 to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Measure for Outcome Severity
N, Mean (SD), Intervention
N, Mean (SD), Control
SMD (95% CI)
All CBD
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Pain Impact on Daily Activities NR NR 0.41 (-0.11, 0.94)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day HAQ-DI 68, 0.13 (0.38) 61, 0.10 (0.46) 0.07 (-0.27, 0.42)
Pramhas, 2023 MP 8 Purified 600 mg/day WOMAC physical function 43, -1.50 (2.84) 43, -1.70 (2.84) -0.02 (-0.45, 0.40)
Subgroup, PL (p = 0.429, I² = 0.0%) 0.11 (-0.15, 0.41)
1:2 ratio THC:CBD
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Pain Impact on Daily Activities NR NR 0.29 (-0.21, 0.80)
Subgroup, PL (I² = 0.0%) 0.29 (-0.21, 0.80)
-1
0
1
Favors Intervention
Favors Control

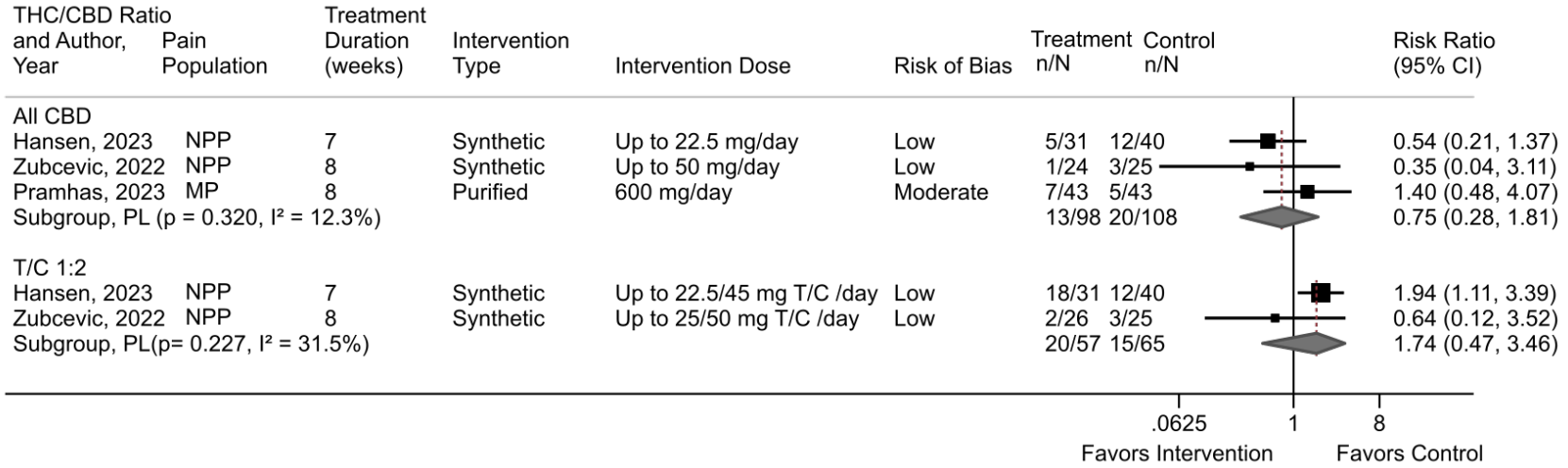
Abbreviations: CBD = cannabidiol; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire – Disability Index; MP = musculoskeletal pain; NPP = neuropathic pain; NR = not reported; PL = profile likelihood; SMD = standard mean difference; T:C = THC to CBD ratio; THC = tetrahydrocannabinol; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Figure D-30. Study withdrawal due to adverse events separated by intervention type for low THC versus placebo (short-term, 1 to 6 months followup)


THC/CBD Ratio and Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 0/31 1/40 0.43 (0.02, 10.14)
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Low 2/27 0/30 5.54 (0.28, 110.42)
Vela, 2022 MP 12 Synthetic 20 to 30 mg/day Moderate 0/70 2/66 0.19 (0.01, 3.86)
Pramhas, 2023 MP 8 Plant-derived 600 mg/day Moderate 9/43 6/43 1.50 (0.58, 3.85)
Subgroup, PL (p = 0.38, I² = 1.1%) 11/171 9/179 1.30 (0.34, 3.33)
T/C 1:2
Hansen, 2023 NPP 7 Synthetic Up to 22.5/45 mg T/C /day Low 3/31 1/40 3.87 (0.42, 35.43)
Zubcevic, 2022 NPP 8 Synthetic Up to 25/50 mg T/C /day Low 4/30 0/30 9.00 (0.51, 160.17)
Subgroup, PL (p = 0.49, I² = 0.0%) 7/61 1/70 5.30 (0.69, 46.52)
.016
1
64
Favors Intervention
Favors Control

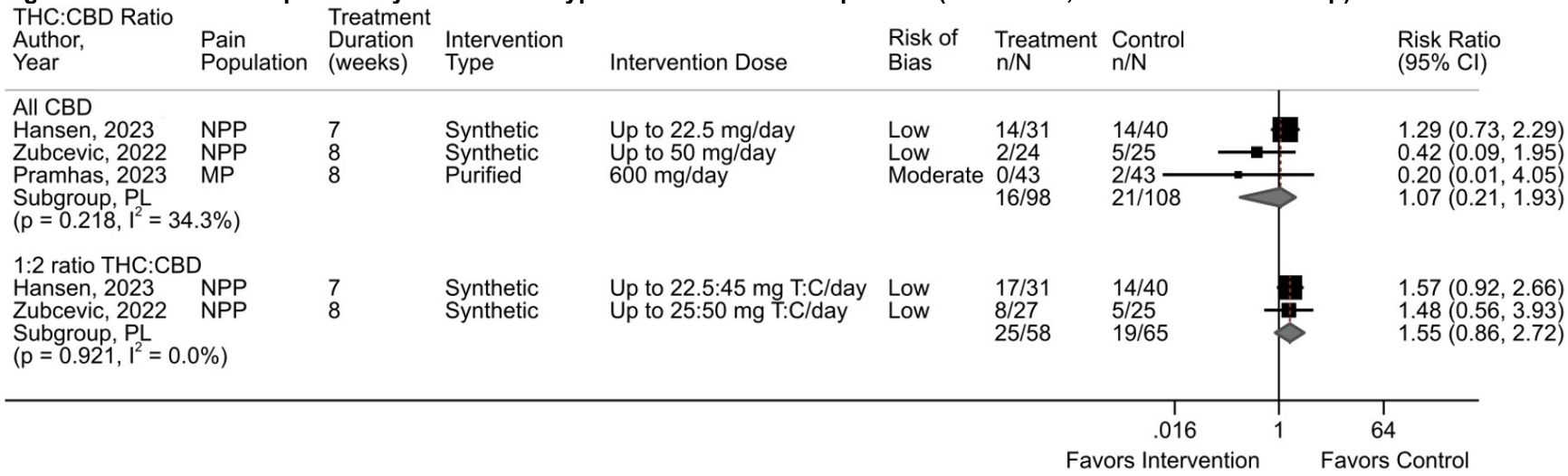
Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

Figure D-31. Dizziness separated by intervention type for low THC versus placebo (short-term, 1 to 6 months followup)


THC/CBD Ratio and Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 5/31 12/40 0.54 (0.21, 1.37)
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Low 1/24 3/25 0.35 (0.04, 3.11)
Pramhas, 2023 MP 8 Purified 600 mg/day Moderate 7/43 5/43 1.40 (0.48, 4.07)
Subgroup, PL (p = 0.320, I² = 12.3%) 13/98 20/108 0.75 (0.28, 1.81)
T/C 1:2
Hansen, 2023 NPP 7 Synthetic Up to 22.5/45 mg T/C /day Low 18/31 12/40 1.94 (1.11, 3.39)
Zubcevic, 2022 NPP 8 Synthetic Up to 25/50 mg T/C /day Low 2/26 3/25 0.64 (0.12, 3.52)
Subgroup, PL(p= 0.227, I² = 31.5%) 20/57 15/65 1.74 (0.47, 3.46)
.0625
1
8
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

Figure D-32. Sedation separated by intervention type for low THC versus placebo (short-term, 1 to 6 months followup)


THC:CBD Ratio
Author, Year
Pain Population
Treatment Duration (weeks)
Intervention Type
Intervention Dose
Risk of Bias
Treatment n/N
Control n/N
Risk Ratio (95% CI)
All CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5 mg/day Low 14/31 14/40 1.29 (0.73, 2.29)
Zubcevic, 2022 NPP 8 Synthetic Up to 50 mg/day Low 2/24 5/25 0.42 (0.09, 1.95)
Pramhas, 2023 MP 8 Purified 600 mg/day Moderate 0/43 2/43 0.20 (0.01, 4.05)
Subgroup, PL 16/98 21/108 1.07 (0.21, 1.93)
(p = 0.218, I² = 34.3%)
1:2 ratio THC:CBD
Hansen, 2023 NPP 7 Synthetic Up to 22.5:45 mg T:C/day Low 17/31 14/40 1.57 (0.92, 2.66)
Zubcevic, 2022 NPP 8 Synthetic Up to 25:50 mg T:C/day Low 8/27 5/25 1.48 (0.56, 3.93)
Subgroup, PL 25/58 19/65 1.55 (0.86, 2.72)
(p = 0.921, I² = 0.0%)
.016
1
64
Favors Intervention
Favors Control

Abbreviations: CBD = cannabidiol; CI = confidence interval; MP = musculoskeletal pain; NPP = neuropathic pain; PL = profile likelihood; T:C = THC to CBD ratio; THC = tetrahydrocannabinol

Appendix E. Evidence Tables

Shown in associated Excel files at https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review.

Appendix F. Risk of Bias Assessment

Shown in associated Excel files at https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review.

Appendix G. Details on Strength of Evidence

Table G-1. Key Questions 1 and 2: Cannabinoids to treat chronic pain – extracted comparable THC to CBD ratio oromucosal spray

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Pain response (≥30% improvement from baseline)	4 RCTs (N=733)[1-4]	Moderate	Direct	Consistent	Imprecise	Unknown	Potential small effect, not statistically significant, with THC:CBD 38% versus 31%, RR 1.18 (0.93 to 1.71); I^2=36%	Low
Comparable THC to CBD Ratio vs. Placebo	Pain severity (change)	7 RCTs (N=878)[1-7]	Moderate	Direct	Consistent	Precise	Unknown	Small benefit with THC:CBD 0 to 10 scale, MD −0.54 (−0.95 to −0.19; I^2=39%) Subgroup analysis removing high risk of bias studies: Moderate benefit MD -0.63 (−1.15 to −0.24; I^2=52%)	Moderate
Comparable THC to CBD Ratio vs. Placebo	Function or Disability	6 RCTs (N=616) [1-5,7]	Moderate	Direct	Consistent	Precise	Unknown	No effect MD −0.42, 95% CI –0.73 to −0.16, I^2=32% (scale 0 to 10)	Moderate
Comparable THC to CBD Ratio vs. Placebo	WAEs	5 RCTs (N=834)[1,2,4,5,7]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 12.5% vs. 10.2%, RR 1.14 (0.65 to 3.02); I^2=51%	Low
Comparable THC to CBD Ratio vs. Placebo	SAEs	3 RCTs (N=866)[2,5]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect 5.0% vs. 4.3%, RR 1.18 (0.26 to 3.4; I^2=0%)	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Comparable THC to CBD Ratio vs. Placebo	Dizziness	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD 31% vs. 8%, RR 3.57 (2.42 to 5.60; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Nausea	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with THC:CBD 14% vs. 7.5% RR 1.79 (1.19 to 2.77; I^2=0%)	Low
Comparable THC to CBD Ratio vs. Placebo	Sedation	6 RCTs (N=866)[1,2,4-7]	Moderate	Direct	Consistent	Imprecise	Unknown	Large effect with THC:CBD RR 5.04 (2.10 to 11.89; I^2=0%)	Low

Abbreviations: BPI-SF = Brief Pain Inventory – Short Form; CBD = cannabidiol; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-2. Key Questions 1 and 2: Cannabinoids to treat chronic pain – synthetic or purified, oral high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Synthetic or Plant Purified THC vs. Placebo	Pain response (≥30% improvement from baseline)	3 RCTs (N=143)[8-10]	Low	Direct	Very serious inconsistency	Imprecise	Unknown	Unable to assess, due to inconsistency from three trials (one trial of nabilone, 85% vs. 38%, RR 2.20 [1.06 to 4.55] and two trials of dronabinol, 43% vs. 57%, RR 0.76 (0.45 to 1.28) and 29% vs. 46%, RR 0.64 [0.31 to 1.31]) Pooled estimate RR: 0.99 (0.43 to 2.37)	Insufficient
Synthetic or Plant Purified THC vs. Placebo	Pain severity	8 RCTs (N=507)[8-15]	Moderate	Direct	Consistent	Imprecise	Unknown	Small effect with synthetic THC 0 to 10 scale, MD −0.78 (−1.59 to −0.08; I^2=64%)	Low
Synthetic or Plant Purified THC vs. Placebo	Function/disability	3 RCTs (N=unclear)[8,9,14] 1 RCT (N=13) not Included in meta-analysis[15]	Moderate	Direct	Consistent	Imprecise	Unknown	No effect (scale 0 to 10) MD: −0.18, −1.25 to 0.77, I^2=51%)	Low
Synthetic or Plant Purified THC vs. Placebo	WAEs	6 RCTs (N=487)[9-14]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect 14% vs. 7%, RR 1.92 (1.10 to 4.80; I^2=0%)	Low
Synthetic or Plant Purified THC vs. Placebo	SAEs	2 RCTs (N=312)[10,12]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 9% vs. 6%, RR 1.53 (0.52 to 4.15)	Insufficient

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Synthetic or Plant Purified THC vs. Placebo	Dizziness	4 RCTs (N=425)[9-12]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 33% vs. 15%, RR 2.30 (1.53 to 3.52; I^2=22%)	Moderate
Synthetic or Plant Purified THC vs. Placebo	Nausea	4 RCTs (N=425)[9-12]	Low	Direct	Consistent	Imprecise	Unknown	Large effect with dronabinol 12% vs. 6%, RR 2.12 (1.09 to 3.96; I^2=0%)	Low
Synthetic or Plant Purified THC vs. Placebo	Sedation	5 RCTs (N=458)[9-13]	Moderate	Direct	Consistent	Imprecise	Unknown	Moderate effect with dronabinol 24% vs. 16%, RR 1.57 (1.11 to 2.29; I^2=0%)	Low

Abbreviations: CBD = cannabidiol; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-3. Key Questions 1 and 2: Cannabinoids to treat chronic pain – extracted, oral or sublingual high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Extracted THC vs. Placebo	Pain severity	2 RCTs (N=294)[16,17]	Moderate	Direct	Inconsistent	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD −1.97 (−5.91 to 1.21; I^2=72%)	Insufficient
	Function/disability	1 RCT (N=18)[17]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 1.75 (−0.46 to 3.98)	Insufficient
	WAEs	1 RCT (N=277)[16]	Moderate	Direct	Unknown	Imprecise	Unknown	Large increased risk 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Low
	SAEs	1 RCT (N=277)[16]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 4.9% vs. 2.2%, RR 2.19 (0.58 to 8.28)	Insufficient
	Dizziness	1 RCT (N=277)[16]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect 62.2% vs. 7.5%, RR 8.34 (4.53 to 15.34)	Low

Abbreviations: CBD = cannabidiol; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-4. Key Questions 1 and 2: Cannabinoids to treat chronic pain – combined (synthetic, purified, or extracted) high THC to CBD ratio products

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Combined (synthetic, purified, or extracted high THC to CBD ratio products	Pain severity	10 RCTs (N=801)[8-17]	Moderate	Direct	Consistent	Precise	Unknown	Moderate effect MD −0.98 (−1.80 to −0.32; I^2=68%)	Moderate

Abbreviations: CBD = cannabidiol; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; SOE = strength of evidence; THC = tetrahydrocannabinol.

Table G-5. Key Questions 1 and 2: Cannabinoids to treat chronic pain – whole plant cannabis

Comparison	Outcome	Number of Studies and Total Participants (N)	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Whole Plant Cannabis (Standardized to 12% THC) vs. Usual Care	Pain Severity change	1 cohort study (N=431, 302 contribute to pain outcome)[18]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 0 to 10 scale, Adjusted MD at 12 months: −1.10 (−1.56 to −0.72)	Insufficient
	WAE	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Large effect with cannabis 4.7% vs. 0%, RR 21.10 (1.24 to 357.80)	Insufficient
	SAE	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	No effect 13% vs. 19%, OR 0.64 (0.38 to 1.04)	Insufficient
	Dizziness	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect 12.6% vs. 9.7%, RR 1.29 (0.75 to 2.21)	Insufficient
	Nausea	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Moderate effect 16.7% vs. 9.7%, RR 1.72 (1.04 to 2.85)	Insufficient
	Sedation	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.5% vs. 4.63%, RR 2.91 (1.46 to 5.83)	Insufficient
	Cognitive Disorder	1 cohort study (N=431)[18]	High	Direct	Unknown	Imprecise	Unknown	Large effect 13.9% vs. 5.7%, RR 3.12 (1.54 to 6.33)	Insufficient

Abbreviations: CI = confidence interval; MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-6. Key Question 1: Cannabinoids to treat chronic pain – synthetic or purified, oral low THC to CBD ratio products

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Oral Synthetic or Plant Purified CBD	Pain severity (change)	4 RCTs (N=334) [9,10,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Not improved MD 0.40 (−0.14 to 1.00)	Moderate
	Pain response (≥30% improvement from baseline)	4 RCTs (N=334) [9,10,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Likelihood not increased RR 0.84 (0.62 to 1.10)	Moderate
	Function/disability	3 RCTs (N=272) [9,19,20]	Low	Direct	Consistent	Imprecise	Unknown	Not improved SMD 0.11 (−0.14 to 0.41)	Moderate
	Any AE	2 RCTs (N=205) [19,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increase risk RR 1.12 (0.93 to 1.49)	Low
	SAEs	2 RCTs (N=190) [10,19]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.70 (0.07 to 4.85)	Insufficient
	WAEs	4 RCTs (N=350) [9,10,19,20]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 1.30 (0.34 to 3.33)	Insufficient
	Sedation	3 RCTs (N=206) [9,10,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increased risk RR 1.07 (0.21 to 1.93)	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
	Nausea	2 RCTs (N=157)[10,20]	Moderate	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.85 (0.22 to 3.65)	Insufficient
	Dizziness	3 RCTs (N=206)[9,10,20]	Moderate	Direct	Consistent	Imprecise	Unknown	No or minimal increased risk RR 0.75 (0.28 to 1.81)	Low
Oral purified THC + synthetic or purified CBD	Pain severity (change)	2 RCTs (N=123)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Not improved MD 0.12 (−0.71 to 0.93)	Low
	Pain response (≥30% improvement from baseline)	2 RCTs (N=123)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Not improved RR 1.07 (0.73 to 1.57)	Low
	Function/disability	1 RCT (N=60)[9]	Low	Direct	Unable to assess	Very imprecise	Unknown	Not improved SMD 0.29 (−0.21 to 0.80)	Low
	Any AE	No studies	--	--	--	--	--	--	No evidence
	SAEs	2 RCTs (N=131)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 0.82 (0.04 to 20.18)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
	WAEs	2 RCTs (N=131)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect RR 5.30 (0.69 to 46.52)	Insufficient
	Sedation	2 RCTs (N=123) [9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Potential increased risk RR 1.55 (0.86 to 2.72)	Low
	Nausea	2 RCTs (N=123) [9,10]	Low	Direct	Consistent	Imprecise	Unknown	Increased risk RR 3.80 (1.08 to 17.05)	Moderate
	Dizziness	2 RCTs (N=122)[9,10]	Low	Direct	Consistent	Very imprecise	Unknown	Potential increased risk RR 1.74 (0.47 to 3.46)	Low
Topical (intraoral) CBD, unclear source	Pain severity (change)	1 RCT (n=60)[21]	Moderate	Direct	Unable to assess	Imprecise	Unknown	Unable to assess due to single small study with methodological limitations 2.0 (IQR 3.0) or 3.5 (2.0) vs. 5.5 (3.0)	Insufficient
Low THC to CBD (Sublingual oil) vs. Placebo	Pain severity (change)	1 RCT (N=15)[22]	High	Direct	Unknown	Imprecise	Unknown	Unable to demonstrate or exclude a positive effect	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Low THC to CBD (Topical CBD) vs. Placebo	Pain severity (change)	1 RCT (N=29)[23]	High	Direct	Unknown	Imprecise	Unknown	Unable to demonstrate or exclude a positive effect	Insufficient

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; CBD = cannabidiol; CI = confidence interval; IQR = interquartile range; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Table G-7. Key Questions 1 and 2: Cannabinoids to treat chronic pain – other or mixed cannabinoids

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Medical cannabis use vs. Non-use	Arrhythmia	1 cohort study (N=32,332)[24]	Moderate	Direct	Unknown	Precise	Unknown	Increased risk Adjusted RR 2.07 (1.34 to 2 .80)	Insufficient
Medical cannabis use vs. Non-use	Acute coronary syndrome	1 cohort study (N=32,332)[24]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect Adjusted RR 1.20 (0.35 to 2.04)	Insufficient
CBDV vs. Placebo	Pain Response (≥30% improvement from baseline)	1 RCT (N=31)[25]	Moderate	Direct	Unknown	Imprecise	Unknown	Large effect, favors placebo 38% vs. 81%, RR 0.46 (95% CI 0.24 to 0.91)	Insufficient
CBDV vs. Placebo	Pain severity (change)	1 RCT (N=31)[25]	Moderate	Direct	Unknown	Imprecise	Unknown	Failed to demonstrate or exclude a detrimental effect MD 0.62 (−0.05 to 1.32)	Insufficient
THC:CBD:CBN vs. Placebo	Pain severity (change)	1 RCT (N=93)[26]	Moderate	Direct	Unknown	Imprecise	Unknown	Moderate effect MD −17.28 (−21.49 to −13.07)	Insufficient
THC:CBD:CBN vs. Placebo	Any AE	1 RCT (N=93)[26]	Moderate	Direct	Unknown	Imprecise	Unknown	No or minimal increased risk 10% vs. 10%, RR 1.0 (0.31 to 3.24)	Insufficient
Hemp seed oil vs. Placebo	Pain severity (change)	1 RCT (N=60)[27]	Moderate	Direct	Unknown	Imprecise	Unknown	Moderate effect MD 1.77 (1.37 to 2.17)	Insufficient
Hemp seed oil vs. Placebo	Function/disability	1 RCT (N=60)[27]	Moderate	Direct	Unknown	Imprecise	Unknown	Small effect MD 7.04 (4.09 to 10.0)	Insufficient

Abbreviations: CBDV = cannabidivarin; CBN = cannabinol; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence.

Table G-8. Key Questions 1 and 2: Observational studies of cannabinoids to treat chronic pain – unknown THC to CBD ratio (patient choice)

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Unknown THC to CBD Ratio vs. Usual Care	Pain response (≥30% improvement from baseline)	No studies	NA	NA	NA	NA	NA	NA	No evidence
Unknown THC to CBD Ratio vs. Usual Care	Pain severity (change) Short-term (3 months)	2 cohort studies: short- to intermediate-term (N=202)[28,29]	High	Direct	Inconsistent	Imprecise	Unknown	VAS (0-100): 41.5 vs 43.6 at 3 months[28] 34.1 vs 48.8; mean difference −14.71 (95% CI, −32.71 to 3.29)[29]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Long-term (12 months)	1 cohort (N=1,514)[30]	High	Direct	Unknown	Precise	Unknown	Adjusted mean; BPI, 0-10 scale) 5.2 vs. 4.9; Beta: 0.37 (95% CI −0.23 to 1.10), p=0.20[30]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care	Function or Disability (SF-36 Physical Function)	2 cohort studies (N=202)[28,29]	High	Direct	Consistent	Imprecise	Unknown	SF-36 Physical Functioning (mean, 0 to 100 scale) 46.5 vs. 43.7 at 6 months[28] 70.0 vs. 69.4; MD 0.56 (95% CI −17.2 to 18.3) at 3 months[29]	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	WAEs	1 cohort study, short- and intermediate-term (N=156)[28]	Moderate	Direct	Unknown	Imprecise	Unknown	6 months: 23% (12/52) vs. 9% (5/55), RR 2.54 (95% CI 0.95 to 6.71)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency	Precision	Publication Bias	Main Findings Effect Size (95% CI)	SOE Grade
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	SAEs	1 cohort study, short- and intermediate-term (N=156)[28]	Moderate	Direct	Unknown	Imprecise	Unknown	None in any group	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs Gabapentin Alone)	Dizziness	1 cohort study, short- and intermediate-term (N=156)[28]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 33% (17/52) vs. 29% (16/55), RR 1.12 (95% CI 0.64 to 1.98) 6 months: 39% (20/52) vs. 33% (18/55), RR 1.17 (95% CI 0.70 to 0.91)	Insufficient
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + gabapentin vs. Gabapentin Alone)	Nausea	No studies	NA	NA	NA	NA	NA	NA	No evidence
Unknown THC to CBD Ratio vs. Usual Care (Nabilone + Gabapentin vs. Gabapentin Alone)	Sedation	1 cohort study, short- and intermediate-term (N=156)[28]	Moderate	Direct	Unknown	Imprecise	Unknown	3 months: 54% (28/52) vs. 33% (18/55) RR 1.65 (95% CI 1.04 to 2.59) 6 months: 60% (31/52) vs. 36% (20/55) RR 1.64 (95% CI 1.08 to 2.48)	Insufficient

Abbreviations: BPI-SF = Brief Pain Inventory – Short Form; CBD = cannabidiol; CI = confidence interval; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event.

Appendix G References

1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.
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Appendix H. Excluded Studies List

1. Medicinal Cannabis for Painful HIV Neuropathy. 2005. **Exclusion reason:** Ineligible publication type
2. Cannabis for Inflammatory Bowel Disease. 2009. **Exclusion reason:** Ineligible publication type
3. Vaporized Cannabis for chronic pain associated with Sickle Cell Disease. Cannabinoid-based therapy and approaches to quantify pain in Sickle Cell disease. 2013. **Exclusion reason:** Ineligible publication type
4. Safety and Efficacy of Medical Cannabis Oil in the Treatment of Patients With Chronic Pain. 2017. **Exclusion reason:** Ineligible publication type
5. Cannabis Oil for Chronic Non-Cancer Pain Treatment. 2018. **Exclusion reason:** Ineligible publication type
6. Cannabis Oil for Pain in Parkinson's Disease. 2018. **Exclusion reason:** Ineligible publication type
7. Cannabis-opioid interaction in the treatment of Fibromyalgia pain; an open label proof of concept study with randomization between treatment groups: Cannabis, Oxycodone or Cannabis/Oxycodon combination. 2019. **Exclusion reason:** Ineligible study design
8. Myorelaxant Effect of Cannabis Cream Topical Skin Application in Patients With TMD. 2019. **Exclusion reason:** Ineligible publication type
9. Safety and Efficacy of Oral Cannabis in Chronic Spine Pain. 2021. **Exclusion reason:** Ineligible publication type
10. Proof of concept trial of Cannabis derivatives in neuropathic pain. Proof of Concept Trial of Cannabis Derivatives in Neuropathic Pain. 2022. **Exclusion reason:** Ineligible publication type
11. Topical CBD for musculoskeletal pain. Immediate effect of topical CBD for Musculoskeletal pain. 2022. **Exclusion reason:** Ineligible publication type
12. Cannabinoids for the Reduction of Inflammation and Sickle Cell Related Pain. Dronabinol for the Reduction of Chronic Pain and Inflammation in People With Sickle Cell Disease. 2022. **Exclusion reason:** Ineligible publication type
13. A Phase III study to investigate the effect of EMD-RX5 on symptoms of psychological distress in adults with chronic pain. A multi-site, parallel-arm, randomised, double blind, placebo-controlled study to investigate the effect of EMD-RX5 on symptoms of psychological distress in adults with chronic pain. 2022. **Exclusion reason:** Ineligible publication type
14. Comparison of VER-01 to Opioids in Patients With Chronic Non-specific Low Back Pain. Multicentre, Randomized, Open-label Study to Prove an Additional Benefit of the Full-spectrum Cannabis Extract VER-01 Over Opioids in the Treatment of Patients With Chronic Non-specific Low Back Pain. 2022. **Exclusion reason:** Ineligible publication type
15. Effects of Cannabidiol (CBD) on Resting-state Electroencephalography (EEG) and Neuropathic Pain Severity in People With Spinal Cord Injury (SCI). 2022. **Exclusion reason:** Ineligible publication type
16. The Impact of THC on Pain Modulation in Fibromyalgia. 2022. **Exclusion reason:** Ineligible publication type
17. Clinical study to prove that treatment of chronic (non-specific) low back pain with VER-01, a cannabis based medicine, shows benefit compared to treatment with opioids. 2022. **Exclusion reason:** Ineligible publication type
18. Diabetic Neuropathic Pain Relief, 6 Weeks Dosage Sublingual Water-soluble CBD/PEA. A Randomized, Double-Blind, Placebo-Controlled Trial Using Cannabidiol and Palmitoylethanolamide for the Treatment of Painful Diabetic Peripheral Neuropathy of the Feet. 2023. **Exclusion reason:** Ineligible publication type

19. A Double-Blind, Randomised Placebo-Controlled Feasibility Trial Assessing Oral Cannabis for The Relief of Fibromyalgia Symptoms. 2023. **Exclusion reason:** Ineligible publication type

20. A Randomised, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Evaluate the Efficacy, Safety and Tolerability of 150 mg Sublingual Cannabidiol in Adults with Mild-to-Moderate Pain. 2023. **Exclusion reason:** Ineligible publication type

21. Safety and Effect on Pain and Function According to RAPID-3 of IHL-675A in Patients With Rheumatoid Arthritis. A Phase II, Blinded, Randomised, Placebo Controlled Clinical Trial to Determine the Safety and Effect on Pain and Function According to RAPID-3 of IHL-675A in Patients With Rheumatoid Arthritis. 2023. **Exclusion reason:** Ineligible publication type

22. Cannabinoid in cancer pain management. A double-blind, randomized, placebo-controlled, parallel arm study evaluating the safety and efficacy of cannabinoid-containing formulations in cancer pain management along with improvement in quality of life of patients with solid tumors. - Nil. 2023. **Exclusion reason:** Ineligible population

23. The efficacy and safety of Cannabis Extract in muscle pain control. Evaluation of the efficacy and safety of Full Spectrum Cannabis Extract, in pain control, in patients with Muscular Temporomandibular Disorder Clinical, randomized, double-blind, placebo-controlled trial. 2023. **Exclusion reason:** Ineligible publication type

24. The Effectiveness of CBD and CBN in the Treatment of Facial Pain and Headache of Muscular Origin. The Evaluation of the Effectiveness of Cannabidiol (CBD) and Cannabinol (CBN) Oral Solutions in the Treatment of Facial Pain and Headache of Muscular Origin. 2023. **Exclusion reason:** Ineligible publication type

25. Investigating the effects of a cannabis-based medication on sleep problems in chronic pain. Long-term effects of a cannabis-based medication on insomnia in chronic back pain: a randomized crossover trial. 2023. **Exclusion reason:** Ineligible publication type

26. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Traumatic or Post-operative Peripheral Neuropathy. 2023. **Exclusion reason:** Ineligible publication type

27. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Central Neuropathy of Any Genesis. 2023. **Exclusion reason:** Ineligible publication type

28. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Back Pain. 2023. **Exclusion reason:** Ineligible publication type

29. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Traumatic or Post-operative Peripheral Neuropathy. 2023. **Exclusion reason:** Ineligible publication type

30. Efficacy and Tolerability of AP707 in Patients With Chronic Back Pain. 2023. **Exclusion reason:** Ineligible publication type

31. Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Diabetic Polyneuropathy. 2023. **Exclusion reason:** Ineligible publication type

32. The Study of Effectiveness of Zingiber cassumunar Roxb.(Plai) Mixed Cannabis sativa L. Leaf Oil for Chronic Pain in Elderly.Randomized controlled trial. 2023. **Exclusion reason:** Ineligible publication type

33. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Diabetic Polyneuropathy. 2023. **Exclusion reason:** Ineligible publication type

34. Long Term Efficacy and Tolerability of AP707 in Patients With Chronic Pain Due to Central Neuropathy of Any Genesis. 2023. **Exclusion reason:** Ineligible publication type

35. Effect of local cannabinoid administration on knee osteoarthritis. Effect of local cannabinoid administration on knee osteoarthritis: a randomized triple-blind placebo based clinical trial. 2023. **Exclusion reason:** Ineligible publication type

36. Cannabidiol for Postoperative Opioid Reduction in Primary Total Knee Arthroplasty. 2024. **Exclusion reason:** Ineligible publication type

37. Topical CBD's Effects on Soreness and Performance. 2024. **Exclusion reason:** Ineligible publication type

38. MIVetsCan: cannabidiol (CBD)-Care Trial. 2024. **Exclusion reason:** Ineligible publication type

39. The effect of Cannabinoid use on Neuropathic Pain in Low Back Pain. 2024. **Exclusion reason:** Ineligible publication type

40. The Effects and Mechanisms of a High CBD Cannabis Extract (BRC-002) for the Treatment of Pain and Health in Complex Regional Pain Syndrome. 2024. **Exclusion reason:** Ineligible publication type

41. Evaluating the Impact of a Novel Cannabinoid Product for Endometriosis. 2024. **Exclusion reason:** Ineligible publication type

42. Dronabinol as an Adjunct for Reducing Pain. 2024. **Exclusion reason:** Ineligible publication type

43. Abelev S, Warne LN, Benson M, et al. Medicinal Cannabis for the treatment of chronic refractory pain: an investigation of the adverse event profile and health-related quality of life impact of an oral formulation. Med Cannabis Cannabinoids. 2022;5(1):20-31. doi: 10.1159/000521492. PMID: 35950052. **Exclusion reason:** Ineligible comparator

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70. Aviram J, Lewitus GM, Pud D, et al. Specific Phytocannabinoid compositions are associated with analgesic response and adverse effects in chronic pain patients treated with Medical Cannabis. Pharmacol Res. 2021 Jul;169:105651. doi: 10.1016/j.phrs.2021.105651. PMID: 34000362. **Exclusion reason:** Ineligible comparator

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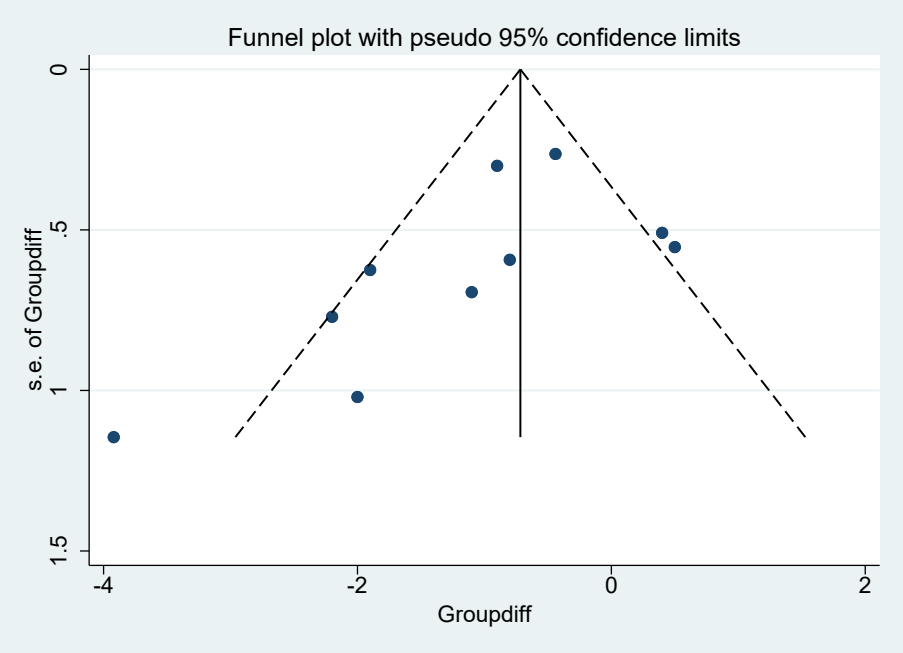
Appendix I. Funnel Plot of High-THC Ratio Studies Included in Meta-Analysis for Pain Severity

Figure I-1. Funnel plot of 10 trials of pain severity for high-THC ratio products versus placebo



Abbreviations: Groupdiff = group difference; SE = standard error; THC = tetrahydrocannabinol.